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Title:

Hyperlipidemia is associated with lower mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity matched cohort study and a meta-analysis

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ABSTRACT

Objective To examine the effect of hyperlipidemia (HLP) on mortality after hospitalization for acute myocardial infarction (AMI) or acute decompensated heart failure (ADHF) and to determine whether HLP modifies the mortality associations of other competing comorbid conditions. A systematic review and meta-analysis to place the current findings in the context of published literature.

Design A retrospective study with 1:1 propensity-score matching cohorts to compare patients with and without HLP; and a meta-analysis.

Setting A large academic center, 1996 to 2015

Participants Hospitalized patients with AMI or ADHF

Main outcomes and measures all-cause mortality and meta-analysis of relative risks (RR).

Results: Unmatched study cohorts: 13,680 patients with AMI (age [mean] 68.5 ± [SD] 13.7 years; 4,710 [34.4%] women, 7,894 [58%] with HLP) and 9,717 patients with ADHF (age, 73.1 ± 13.7 years; 4,109 [42.3%] women, 3,668 [38%] with HLP). After propensity matching 8,696 AMI patients and 5,758 ADHF patients were included. All-cause mortality was observed in 5.9 and 8.6/100 person-years of follow up of matched AMI patients with and without HLP, respectively (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.72 – 0.80). A similar mortality reduction occurred in matched ADHF patients with or without HLP (12.4 vs 16.3 deaths/100 person-years; HR 0.80, 95% CI 0.75 – 0.86). HRs showed modest reductions when HLP occurred concurrently with other comorbid conditions. Meta-analyses of 9 observational studies showed that HLP was associated with lower mortality after incident AMI or ADHF (AMI: RR 0.72, 95% CI 0.69 – 0.76; HF: RR 0.67, 95% CI 0.55 – 0.81)

Conclusions: Among propensity score-matched AMI and ADHF cohorts, concurrent HLP, compared with no HLP, was associated with lower mortality and attenuation of observed mortality associations with

other comorbidities. Together with similar findings from meta-analysis, we support further studies to define appropriate HLP targets in real world patients.

Strengths and limitations of this study

- This is the first study to examine the interaction of hyperlipidemia with other comorbid conditions and its association with long-term mortality after incident acute myocardial infarction or acute decompensated heart failure using propensity score-matched cohorts to account for a number of baseline characteristics.
- The study included a systematic review of the association between hyperlipidemia and mortality after the development of acute myocardial infarction or heart failure and quantified relative risks through meta-analysis.
- After incident acute myocardial infarction or acute decompensated heart failure a diagnosis of hyperlipidemia as compared to no hyperlipidemia was associated with reduced long-term mortality, a longer median survival, and modest attenuation of the magnitude of mortality risk associated with other competing comorbid conditions
- The complementary meta-analysis of published observational studies provides further evidence that hyperlipidemia is associated with decreased mortality following incident acute myocardial infarction or acute decompensated heart failure
- Limitations include inherent disadvantages of retrospective cohort studies, potential unmeasured confounders, *International Classification of Diseases, Ninth Revision, Clinical Modification* to identify study cohorts, ascertainment of comorbid conditions during index hospitalization, and lack of data on subsequent acquisition of these conditions during the follow up.

Introduction

Hyperlipidemia (HLP) is a major modifiable risk factor for the development of acute myocardial infarction (AMI) (1, 2)and lipid lowering by statin decreases the risk of incident AMI and cardiovascular mortality(3, 4). Similar data were reported for incident heart failure (HF)(3-6). Surprisingly, several recent studies found an inverse association wherein HLP, counterintuitively, conferred an overall survival benefit in patients with established AMI (AMI)(7, 8) and HF(9) whereas other studies were contradictory(10, 11). Uncertainty remains for both mortality risks associated with HLP and how HLP affects mortality relationships of other covariates after incident AMI and HF.

We postulated that if a diagnosis of HLP decreases the mortality after AMI or HF, then, it also lessens the magnitude of mortality risks associated with other competing comorbidities. We tested this hypothesis, separately, in large cohorts of patients hospitalized for incident AMI or acute decompensated HF (ADHF). To compare patients with and without HLP, we assembled 1:1 balanced groups using propensity score-matching for each study condition. Our objectives were three-fold: 1) to estimate the association of HLP with all-cause mortality among AMI or ADHF cohorts, 2) to examine whether any observed effect of HLP influences the mortality risk associations with other competing comorbid conditions(12), and 3) to provide risk estimates for mortality associated with HLP after AMI or HF using an aggregated meta-analysis of published and current study data to place the current findings in the context of published literature.

Methods

Cohort study

STUDY POPULATION AND DATA COLLECTION

The study cohorts comprised of adults aged ≥18 years, hospitalized at Mayo Clinic from August 1, 1996 to September 17, 2015 with primary discharge diagnoses of AMI or acute decompensated HF (ADHF) and only the first hospitalization during the study period was included in the analysis. AMI included both ST-elevation myocardial infarction (STEMI) and non-STEMI. ADHF comprised of both heart failure with reduced ejection fraction and those with preserved ejection fraction. Discharge diagnoses were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (presented in supplement table 1). The flow diagram of for the process of selection of study cohorts is presented in supplement figure 1. Further details of data extraction are published elsewhere(13). The study was approved by the Mayo Clinic Institutional Review Board and need for patient consent was waived.

ASCERTAINMENT OF ACUTE MYOCARDIAL INFARCTION AND ACUTE DECOMPENSATED HEART FAILURE

For each patient the primary diagnosis, AMI or ADHF, at the time of discharge were documented by the attending physician, subsequently assigned ICD-9-CM code, and then captured by abstractors.

ASCERTAINMENT OF COMORBID CONDITIONS

We considered a comorbid condition to be present if it was documented as a secondary diagnosis during index hospitalization. We focused on a panel of 20 comorbid conditions (CCs) defined by Department of Health and Human Services (12) and identified by Clinical Classifications Software codes developed by US Healthcare Cost Utilization Project. These CCs are among the most common long-term conditions and most likely to persist indefinitely. CCs with prevalence < 3% were excluded from analysis. To ascertain the comorbid effect of HLP on other concurrent condition, we assembled patients with AMI or ADHF according to concurrent HLP with one of the other comorbid condition within an individual.

ASCERTAINMENT OF HYPERLIPIDEMIA AND STATIN USE

Hyperlipidemia was defined as having a preexisting diagnosis by a physician or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥100 mg/dl as measured during

index hospitalization or within preceding 6-month. LDL-C was measured indirectly by Friedewald method(14). Published reports suggest that lipid panel measured during the first 72 hours after an acute cardiovascular event reliably represents baseline level(15). Statin use was based on discharge medication reconciliation.

ASCERTAINMENT OF MORTALITY

All deaths occurring from admission to censoring date of August 17, 2016 were abstracted from medical record updated by respective primary care provider at Mayo Clinic or Mayo Clinic Health System across southeast Minnesota.

CONSTRUCTION OF PROPENSITY SCORE-MATCHED COHORTS

To mitigate bias from differences in baseline characteristics and to enhance the robustness of inferences, we assembled balanced pairs of patients with or without HLP for each study condition (AMI and HF) using their propensity scores.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in this study

Systematic review and meta-analysis

We searched of MEDLINE, EMBASE, Cochrane Library, Web of Science databases for eligible trials from inception through September 2017 with continued surveillance through February 2018 for trials examining the associations of HLP with mortality. Studies with incomplete data were excluded. Methodological details of the conduct of meta-analysis are published elsewhere(16). The search strategy is presented in the supplement. For all analyses, a 2-side P <0.05 was regarded as statistically significant. The analyses were performed using Statistical Analysis System 9.4 (SAS Institute) version

Statistical analysis

1. THE COHORT STUDY

Student *t* test, Wilcoxon rank-sum test, and χ^2 test were used to compare means, medians, and proportions respectively. Patients were followed up until death or the censoring date of August 17, 2016 whichever came first.

Propensity score analysis(17): We assembled propensity score-matched pairs of patients with AMI or ADHF to balance the differences in baseline variables between patients who have concurrent HLP and those who did not. Propensity scores were estimated using logistic regression (PROC PS MATCH in SAS) based on age, gender, length of hospital stay, race, comorbidities, and time period (1996-2005 vs. 2006-2016). Standardized differences in the matched cohort ranged from 0.122 to 0.004. One-to-one nearest neighbor caliper matching was used to match patients based on the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score. Patients were of exact match on gender, race and enrollment period. Each patient without HLP was matched to one with HLP and generated a quasi-randomized design whereby study groups (HLP vs no HLP) have the same propensity to be allocated to either group.

Kaplan-Meier estimates: Kaplan-Meier estimates were performed using propensity-score matched cohorts and stratified log-rank tests were used to compare survival curves.

Multivariable Cox models: Cox proportional hazards models were performed on the matched samples using a robust variance estimator to account for matching. The Cox models do not include variables that were used for the propensity score matching. Multiple models were constructed for estimating hazard ratios (HR) for mortality. Model 1 estimated HR and 95% confidence intervals (CI) for mortality associated with HLP and other CCs. Model 2 was extended to fit Model 1 plus statin therapy. Model 3 examined the comorbid effect of HLP in combination with other key CCs.

Sub-group analysis: We performed subgroup analysis to ascertain the degree of bias that might explain significant associations between HLP and mortality in balanced cohorts. We examined the association between HLP and all-cause mortality in two clinically important subgroups with available data on 1)

statin therapy on discharge and 2) LDL-cholesterol level on or within 6 month preceding index hospitalization.

2. THE META-ANALYSIS

The random-effects model was used to pool estimates across studies because of anticipated heterogeneity(18). The results were expressed as relative risk (RR) and 95% CI. Heterogeneity was assessed using I^2 to reflect proportion of heterogeneity not attributable to chance(19). The number of studies was insufficient to statistically evaluate publication bias. The characteristics of included studies (Supplement table 2), assessment of risk of bias (supplement table 3), PRISMA flow diagram (Supplement figure 2) are presented in supplement material.

Results

1. THE COHORT STUDY

Cohort study population

The supplemental Figure 1 illustrates the Strengthening the Reporting of Observational Studies in Epidemiology flow diagram for selection of final study cohorts: AMI (Initial cohort n = 13,680; propensity score-matched cohort n = 8,696) and ADHF (Initial cohort n = 9,717; propensity score-matched cohort n = 5,758). All patients were followed up until death or censoring date of August 17, 2016.

Baseline characteristics

Baseline characteristics for each study cohort, before and after propensity score-matching, stratified by the presence or absence of concurrent HLP are presented in Table 1. Before propensity-score matching, the study comprised of 13,680 patients in AMI cohort and 9,717 patients in ADHF cohort. Propensity-

score matching resulted in 8,696 and 5,758 pairs of patients with and without HLP in AMI and ADHF cohorts, respectively. Matched patients in each cohort were balanced on baseline characteristics. In AMI cohort, before matching patients with HLP were younger, more likely to be males, and had low prevalence of COPD and heart failure and high prevalence of CKD and hypertension. As these variables were balanced in propensity score-matching, a balanced cohort with standardized differences of <10% for baseline characteristics was created for final analysis. Supplement figure 3 illustrates a love plot of standardized differences before and after propensity-score matching to allow visualization of improvement in prognostic balance. Of 20 CCs, only 8 were included in final analysis for their frequency ≥3%.

MORTALITY

Acute myocardial infarction: In matched HLP group 2,182 (50.2%) patients had died (Follow up: median 8.8 years, interquartile [IQ] 3.2 – 13.1 years, 37,068 person-years of follow-up) as compared with 2,718 (62.5%) patient in no HLP group (median 6.3 years, IQ 1.4– 12.4 years, 31,569 person-years of follow-up) correspond to 5.9 deaths in HLP group and 8.6 deaths in non-HLP group per 100 person-years of follow up. The median time to death was longer for HLP group than those with no HLP (12.3 vs 8 years, p <0.0001).

Acute decompensated heart failure: In matched HLP group 1,687 (58.6%) patients had died (Follow up: median 3.2 years, IQ 1.0 – 6.9 years, 13,577 person-years of follow-up) as compared with 1,948 (67.7%) patient in no HLP group (median 2.5 years, IQ 0.7 – 6.2 years, 11,951 person-years of follow-up), equated to 12.4 deaths in HLP group and 16.3 deaths in non-HLP group per 100 person-years. The median time to death was longer for HLP group than those with no HLP (5.2 vs 3.5 years, P <0.0001).

KAPLAN-MEIER ESTIMATES

Figure 1 displays Kaplan-Meier estimates of all-cause mortality by the presence or absence of HLP for AMI and ADHF in propensity-score matched cohorts. Kaplan-Meier curves among patients with and without HLP started to diverge soon after discharge and remained parallel throughout the follow up period for both AMI and ADHF. Log-rank *P* value for patients with and without HLP remained < 0.0001 for each index condition. Risk differences in mortality between patients with and without HLP persisted in age <65 and ≥65 years, male and female, white and non-White with log-rank p <0.0001 for all.

COX PROPORTIONAL REGRESSION MODEL 1

The results are presented in Figure 2. An admission diagnosis of HLP as compared with no HLP, was associated with a lower risk of death from any cause after AMI (HR 0.76, 95% confidence interval [CI] 0.72 – 0.80, n = 8,696) or ADHF (HR 0.80, 95% CI 0.75 – 0.86, n = 5,758). The findings did not change significantly with exclusion of patients with a new in-hospital HLP diagnosis in sensitivity analysis. Co-occurrence of cancer, CKD, COPD, diabetes mellitus, HF, or stroke independently increased mortality following AMI or ADHF. Whereas hypertension reduced mortality by 8% (95% CI 0.87 – 0.98) after AMI, neither hypertension nor CAD influenced the mortality following ADHF.

COX PROPORTIONAL REGRESSION MODEL 2

In separate analysis, adjustment of Cox proportional model for statin treatment did not change the results for baseline HLP in predicting the all-cause mortality (AMI: HR 0.69, 95% CI 0.65 - 0.73; ADHF: HR 0.78, 95% CI 0.73-0.83).

COX PROPORTIONAL REGRESSION MODEL 3

The results of Cox model 3 are shown in Figure 2. Magnitude of HRs for mortality associated with cancer, COPD, CKD, diabetes, heart failure, and stroke were all modestly attenuated with concurrent HLP across

study cohorts. By comparison, protective effect of HLP on mortality was enhanced when paired with HTN in both AMI (HR 0.77, 95% CI 0.72- 0.83) and ADHF (HR 0.86, 95% CI 0.78-0.94).

2. META-ANALYSIS

Hyperlipidemia was associated with lower all-cause mortality after AMI (30-day mortality: 3 studies(7, 20), n = 124,912, RR 0.66, 95% CI 0.45 – 0.97; long-term mortality [≥ 2 years]: 2 studies(21), n = 11,161, RR 0.72, 95% CI 0.69-0.76) and ADHF (long-term mortality [≥ 2 years]: 6 studies(22-26), n = 11,166, RR 0.67, 95% CI 0.55 – 0.81). Meta-analysis of AMI was homogenous (I^2 0%) whereas substantial heterogeneity was noted in heart failure meta-analysis reflecting different settings of these observational studies. The results of meta-analysis are presented as forest plots (Figure 3).

Discussion

MAIN FINDINGS

This propensity-score matched study of large cohorts of patients hospitalized for AMI or ADHF and a systematic review with meta-analysis provided a rigorous assessment of the association between HLP and long-term all-cause mortality. First, a diagnosis of HLP, compared to no HLP, was associated with 24% and 20% relative risk reduction in all-cause mortality corresponding to 27 and 39 fewer deaths per 1000 person-years after incident AMI and ADHF, respectively. The reduced mortality associated with HLP was robust to adjustment for potential confounder including demographics, clinical characteristics, and key CCs. The association was consistent across the following subsets: young and old, male and female, white and non-white, and prevailed across both study cohorts. The reductions in mortality were independent of benefit attributable to statin therapy. Additionally, HLP was associated with a longer median time to death. Second, we found that cancer, COPD, CKD, diabetes mellitus, heart failure, or stroke, were all significantly associated with increased long-term mortality. This increased risk was

offset by the lower mortality from HLP resulting in attenuation or even a null effect on long-term mortality in patients with AMI or ADHF who had HLP concurrent with other CCs. By comparison, hypertension which had no effect in HF was inversely associated with mortality in AMI, similar to HLP. The magnitude of mortality reduction associated HLP was enhanced in the presence of HTN after incident AMI and ADHF. Third, the complementary meta-analysis of published observational studies and current study data demonstrated consistent results and provide further evidence that HLP is associated with decreased mortality following incident AMI or ADHF.

COMPARITVE STUDIES

A number of limitations exist for cholesterol hypothesis. The association of HLP with the degree of atherosclerosis is lacking(27). Numerous epidemiological studies have shown an inverse association between HLP and long-term mortality in general population with no pre-existing cardiovascular disease and diabetes(28, 29). An earlier systematic review found that the mortality risk from HLP decreased with increasing age(30). In comparison, we found that HLP maintained its survival benefit even in elderly population, a finding supported by a meta-analysis of 19 cohort studies that showed inverse association between elevated cholesterol and mortality(27). These observations were further supported by widely used risk-prediction models for AMI, and HF in which HLP did not make into the final prediction models (10, 11, 31-33) suggesting a much weaker or no association with mortality. An inverse relationship between HLP and mortality was reported for a number of other disease conditions not the focus of present study(34-36). Similarly, numerous other conditions such as obesity, hypertension, cigarette smoking, and factor V Leiden exhibit epidemiological paradox(37-39). According to epidemiologists, these paradoxes may exemplify collider or index event bias wherein established risk factor for the first occurrence of a disease become inversely associated after the occurrence of an event (40-42). The effect of HLP might be concealed in the presence of stronger competing risk factors for mortality(43). A progressive increase in proportion of deaths from non-cardiovascular conditions with differential

association with baseline cholesterol may be another explanation for an inverse association of HLP with all-cause mortality(44). Numerous investigators argued that low cholesterol represents a biological marker for concurrent cachexia, malnutrition, cancer, and other chronic diseases with proven adverse impact on survival(45, 46). However, HLP remained a favorable predictor of mortality in several studies that even excluded terminal diseases(27). Previous studies reported that even healthy subjects with low cholesterol are especially predisposed to infectious diseases(47-49). Although our findings were adjusted cancer and numerous other CCs, the potential confounding by undiagnosed cachexia or malnutrition cannot be excluded. Our findings were contradicted by a number of randomized clinical trials and meta-analyses of statin therapy in AMI that demonstrated a dose dependent decrease in the risk of cardiovascular events with reduction in LDL-C level, even down to <70 mg/dl(3). These discrepant findings are attributable to demographic differences, select patient population possibly with lower rates of CCs, shorter follow-up intervals, and focus on cardiovascular events including cardiovascular mortality rather than all-cause mortality as the outcome.

CLINCAL IMPLICATIONS

The findings of this study, if validated, should reinforce the importance of HLP in predicting long-term mortality after index AMI or ADHF and potentially provide guidance for subsequent management. Hyperlipidemia can readily be diagnosed and help recognize AMI and HF patients with lower long-term mortality. In these patients, clinical care should not focus on certain lipid targets; rather evidence-based secondary prevention strategies should be initiated. In comparison, patients with AMI and ADHF without HLP may be considered to have increased risk for early mortality and potentially alert providers for close monitoring during hospitalization and after discharge. Both categories of patients would profit from thoughtful tailored programs with distinctive goals of care for existing CCs.

STRENGTHS AND LIMITATIONS

This study has several strengths. Firstly, large study cohorts and high level of case ascertainment for incident events and prompt mortality update(50) allowed precise estimation of mortality risks. Broader range of patient population, long follow-up extending to 20 years, and all-cause rather than cardiovascular mortality as the primary outcome are additional advantages over randomized controlled trials. Secondly, propensity-score matching to balance observed patient-characteristics enabled further control of potential differences. Thirdly, we conducted a systematic review and meta-analysis to place to place the findings of this study in the larger context of existing literature with consistent findings. The study also has a number of important limitations. These included. The possibility of unmeasured confounders, reliance on ICD-9-CM codes to identify study cohort, Clinical Classifications Software codes to assess coexisting CCs, ascertainment of CCs during index hospitalization, and lack of data on subsequent acquisition of these conditions during the follow up. Our study cohorts were homogenous with respect to race and substantially older than those observed in most clinical trials, but, similar to those in many epidemiological studies. The pre-existing hyperlipidemia and CCs were physician-diagnosed during index hospitalization rather than being assigned by study investigators. Meta-analysis of ADHF was associated with heterogeneity; nevertheless, the results from all the included studies suggested a reduction in mortality with HLP. Notwithstanding these limitations, the findings of the present study may be extended to hospital-based, AMI and ADHF population at large.

COCLUSIONS

The current findings, based on large unselected hospital-based patient-populations, provide strong evidence that after incident AMI and ADHF a diagnosis of HLP as compared to no HLP was associated with reduced long-term mortality, a longer median survival, and modest attenuation of the magnitude of mortality risk associated with other competing CCs. Our data support a protective role for HLP against all-cause mortality following incident AMI and ADHF and prompts further studies to understand the

complex relationship between HLP and mortality, especially in the presence of other competing comorbidities and to define appropriate HLP targets to maximize the benefits.

Contributor-ship statement

All co-authors contributed substantially to the conception or design of the work, or the acquisition, analysis or interpretation of data, drafting the work or revising it critically for important intellectual content and all approved the final version to BMJ Open.

Competing interest statement

The authors whose names are listed above in the title page certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Data sharing statement

We declare that this is a retrospective cohort study and all supporting data are available within the article and the online supplement material.

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Table 1: Patient characteristics and standardized differences before and after propensity score-matching

Acute myocardial infarction							
		All Patients, n = 13,680			Propensity score-matched cohort, n = 8,696		
Variables		with Hyperlipidemia N = 8,929	with no hyperlipidemia N = 4,751	Absolute Standardized Difference	with Hyperlipidemia N = 4,348	With no hyperlipidemia N = 4,348	Absolute Standardized Difference
Demographics	Age, y, mean ± SD	67.0 ± 13.6	71.3 ± 13.5	0.315	68.9 ± 13.3	70.5 ± 13.6	0.122
	Male n = (%)	6,035 (68)	2,938 (62)	0.121	2,761 (64)	2,761 (64)	0
	White n= (%)	8,108 (91)	3,963 (83)	0.222	3,744 (86)	3,744 (86)	0
Anthropometric measurements	BMI kg/m^2	30.1 ± 6.2	28.8 ± 6.3	-	29.8 ± 6.3	29.9 ± 6.3	-
	BMI, missing n = (%)	1,556 (17)	1,520 (32)	-	1,274 (29)	1,330 (31)	-
Clinical characteristics	LOS, days, median (quartiles 25%-75%)	3 (2-5)	4 (3-8)	0.275	4 (3-6)	4 (3-7)	0.086
Year of hospital admission	1996-2005 n = (%) 2006-2016 n = (%)	3886 (44) 5043 (57)	3732 (79) 1019 (21)	0.770	3341 (77) 1007 (23)	3341 (77) 1007 (23)	0
Comorbid conditions	CAD, n = (%)	-	-		-	-	
	Cancer, n = (%)	744 (8)	342 (7)	0.042	279 (6)	313 (7)	0.029
	CKD, n = (%)	885 (12)	380 (8)	0.067	348 (18)	353 (8)	0.004
	COPD, n = (%)	820 (9)	640 (14)	0.136	482 (11)	543 (13)	0.044
	Diabetes, n = (%)	2,567 (29)	1,249 (26)	0.055	1,091 (295)	1,149 (26)	0.030
	Heart failure, n = (%)	1,762 (20)	1,376 (29)	0.216	1,033 (24)	1,173 (27)	0.075
	Hypertension, n = (%)	6,049 (68)	2,584 (54)	0.277	2,530 (58)	2,453 (56)	0.037
	Stroke, n = (%)	359 (4)	168 (4)	0.025	151 (4)	148 (3)	0.004
Lipid levels	LDL-C mg/dl	110.9 ± 39.2	78.7 ± 25.0	-	118.4 ± 37.6	78.8 ± 25.1	-
	LDL-C, missing n = (%)	483 (5)	1,356 (29)	-	251 (6)	1,177 (27)	-
Drug treatment	Statin	4,665 (52)	1,431 (30)	0.461	1,566 (36)	1,412 (33)	0.074
Heart Failure							
		All Patients, n = 9,717			Propensity score-matched cohort, n = 5,758		
		With hyperlipidemia N = 3,941	With no hyperlipidemia N = 5,776	Absolute Standardized Difference	With hyperlipidemia N = 2,879	With no hyperlipidemia N = 2,879	Absolute Standardized Difference
Demographics	Age, y, mean ± SD	73.2 ± 12.4	73.0 ± 14.5	0.020	72.6 ± 12.6	73.1 ± 14.1	0.040
	Male n = (%)	2,342 (59)	3,266 (57)	0.058	1,682 (54)	1,682 (54)	0

	White n= (%)	3,574 (91)	4,896 (85)	0.181	2,588 (90)	2,888 (90)	0
Anthropometric measurements	BMI kg/m^2	31.1 ± 7.6	29.7 ± 7.5	-	31.0 ± 7.6	30.0 ± 7.5	-
	BMI, missing n = (%)	193 (5)	780 (13)	-	185 (6)	262 (9)	-
Clinical characteristics	LOS, days, median (quartiles 25%-75%)	4 (2 – 6)	4 (2 – 7)	0.183	4 (2 – 6)	4 (2 – 7)	0.018
Year of hospital admission	1996-2005 n = (%)	1221 (31)	3510 (61)	0.626	1197 (42)	1497 (42)	0
	2006-2016 n = (%)	2720 (69)	2266 (39)		1682 (58)	1682 (58)	
Comorbid conditions	CAD, n = (%)	2,482 (63)	2,309 (40)	0.472	1,580 (55)	1,937 (53)	0.031
	Cancer, n = (%)	595 (15)	736 (13)	0.068	419 (15)	420 (15)	0.001
	CKD, n = (%)	1,286 (33)	1,299 (23)	0.228	802 (28)	819 (28)	0.013
	COPD, n = (%)	813 (21)	1,152 (20)	0.017	567 (20)	584 (20)	0.015
	Diabetes, n = (%)	1,617 (41)	1,660 (29)	0.260	1,117 (39)	1,015 (35)	0.075
	Heart failure, n = (%)	-	-	-	-	-	-
	Hypertension, n = (%)	2,911 (74)	2,930 (51)	0.492	1,931 (67)	1,869 (65)	0.046
	Stroke, n = (%)	160 (4)	106 (2)	0.132	94 (3)	75 (3)	0.039
Lipid levels	LDL-C mg/dl	92.8 ± 39.9	75.5 ± 28.5	-	98.5 ± 41.0	74.0 ± 28.5	-
	LDL-C, missing n = (%)	517 (13)	2,130 (37)	-	268 (13)	928 (32)	-
Drug treatment	Statin	1731 (44)	963 (17)	0.621	906 (32)	890 (28)	0.084

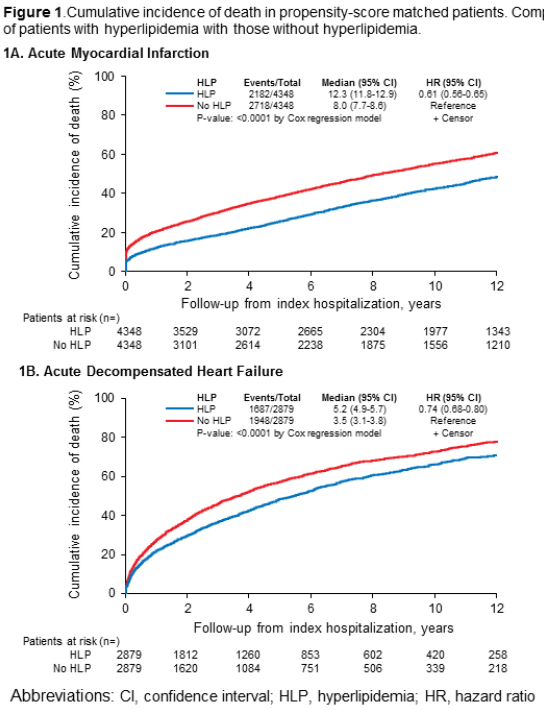
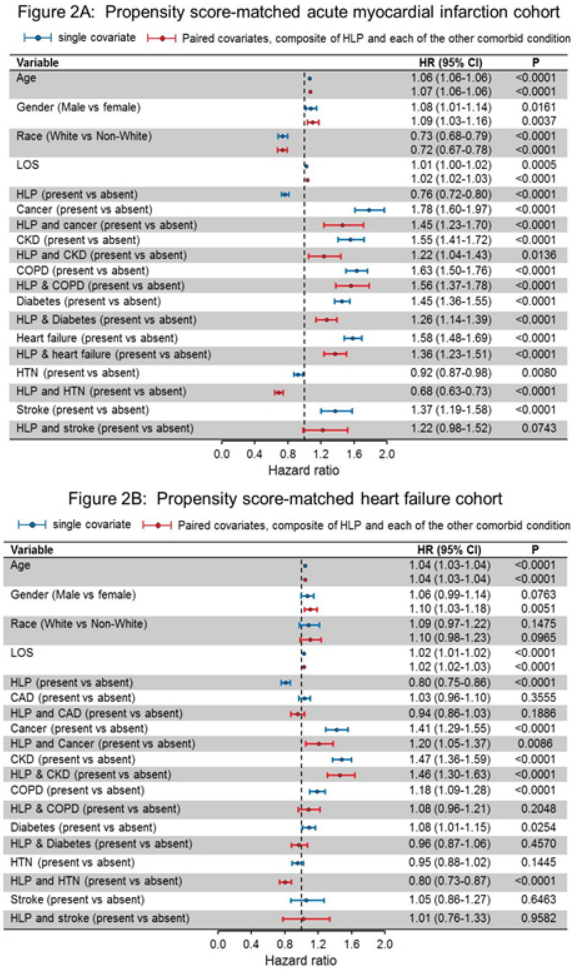


Figure 1.Cumulative incidence of death in propensity-score matched patients. Comparison of patients with hyperlipidemia with those without hyperlipidemia.

254x190mm (96 x 96 DPI)

Figure 2. Forest plot, based on Cox regression analysis by robust variance estimator to account for matching, showing comparison of mortality estimates across specific single covariate and paired covariates, combined hyperlipidemia and one of the other comorbid condition.



Abbreviations: CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HLP, hyperlipidemia; HR, hazard ratio; HTN, hypertension; LOS length of stay

Figure 2. Forest plot, based on Cox regression analysis by robust variance estimator to account for matching, showing comparison of mortality estimates across specific single covariate and paired covariates, combined hyperlipidemia and one of the other comorbid condition.

190x254mm (96 x 96 DPI)

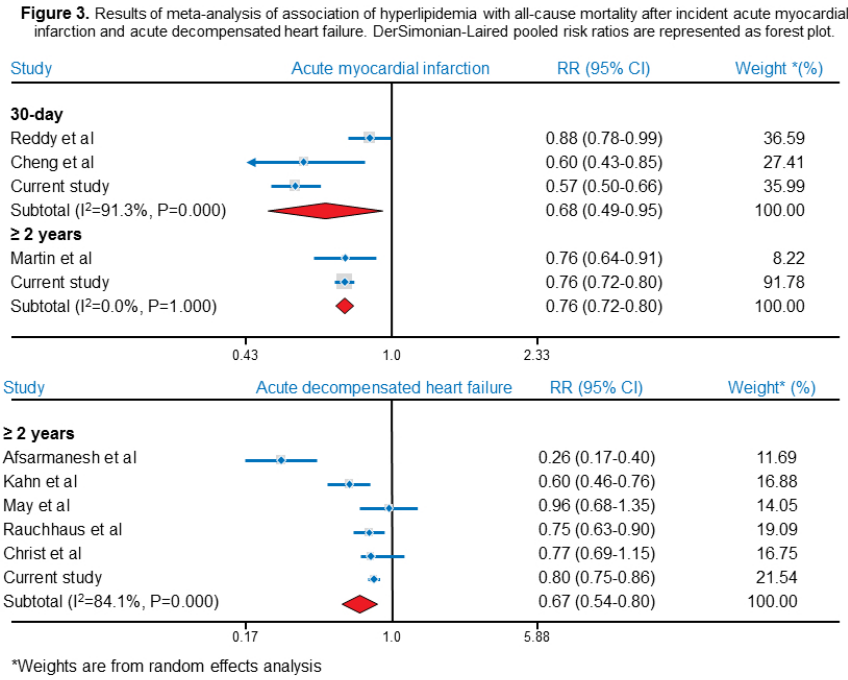


Figure 3. Results of meta-analysis of associations of hyperlipidemia with all-cause mortality after incident acute myocardial infarction and heart failure

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Supplementary Material

Title:

Hyperlipidemia is associated with lower mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity matched cohort study and a meta-analysis

Study coauthors:

Mohammed Yousufuddin, Paul Takahashi, Brittny Major, Eimad M. Ahmmad, Hossam M. Al-Zu'bi, Jessica Shultz, Taylor Doyle, Kelsey Jensen, Umesh Sharma, Zhen Wang, Vinaya Simha, Mohammad H. Murad,

1. **Search strategy**
2. **Supplement Table 1.** *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for two index conditions used in the study
3. **Supplement Table 2.** Characteristics of included studies and participants
4. **Supplement Table 3.** Assessment of risk of bias using Newcastle-Ottawa scale
5. **Supplement Figure 1.** STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram of the process of selection of study cohorts
6. **Supplement Figure 2.** PRISMA flow diagram of evidence search and selection of studies for meta-analysis
7. **Supplement Figure 3.** Supplemental figure 3. Love plot showing standardized differences for baseline covariates comparing original propensity-score unmatched to propensity-score matched samples, acute myocardial infarction cohort (left panel) and heart failure cohort (right panel)

SEARCH STRATGY

Ovid search strategy

Database(s): Embase 1988 to 2018 Week 08, EBM Reviews - Cochrane Central Register of Controlled Trials January 2018, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp Myocardial Infarction/	464828
2	exp heart infarction/	293249
3	(("coronary arter*" adj3 occlusion) or (heart adj2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*").ti,ab,hw,kw.	606258
4	1 or 2 or 3	608529
5	acute.ti,ab,hw,kw. and 4	239685
6	exp Heart Failure/	498877
7	(((heart or cardiac or myocardial) adj2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis").ti,ab,hw,kw.	519250
8	6 or 7	633042
9	exp Pneumonia/	313860
10	("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*").ti,ab,hw,kw.	533949
11	9 or 10	549542
12	5 or 8 or 11	1350218
13	exp Hyperlipidemias/	192450
14	("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous	252850

	xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex").ti,ab,hw,kw.	
15	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu, dt	80348
16	(Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*).ti,ab,hw,kw.	208226
17	Dyslipidemias/	20270
18	(dyslipidemia or dyslipoproteinemia).ti,ab,hw,kw.	92147
19	or/13-18	481133
20	12 and 19	47704
21	exp survival/	902536
22	exp death/	717663
23	exp mortality/	1191292
24	mortality.fs.	506650
25	exp survival analysis/	274790
26	(surviv* or death* or mortalit* or fatalit*).ti,ab,hw,kw.	5314876
27	or/21-26	5623459
28	20 and 27	24286
29	(exp animals/ or exp nonhuman/) not exp humans/	8998409
30	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.	7727415
31	28 not (29 or 30)	23991

32	limit 31 to english language	22671
33	limit 32 to (conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,CCTR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	4951
34	32 not 33	17720
35	exp controlled study/	5856381
36	exp Randomized Controlled Trial/	924372
37	exp triple blind procedure/	179
38	exp Double-Blind Method/	405536
39	exp Single-Blind Method/	72408
40	exp latin square design/	348
41	exp Placebos/	330956
42	exp Placebo Effect/	10111
43	exp comparative study/	2771403
44	exp intervention studies/	34956
45	exp Cross-Sectional Studies/	500737
46	exp Cross-Over Studies/	128902
47	exp Cohort Studies/	2186646
48	exp longitudinal study/	344882
49	exp retrospective study/	1277886
50	exp prospective study/	963919
51	exp clinical trial/	2029131
52	clinical study/	106532
53	exp case-control studies/	1046859
54	exp confidence interval/	162834
55	exp multivariate analysis/	475730
56	((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (random* adj1 allocat*) or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or	18012184

	((study or trial or random* or control*) and compar*)).mp,pt.	
57	or/35-56	18453897
58	34 and 57	14467
59	exp *Hyperlipidemias/ or exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu, dt or *Dyslipidemias/ or ("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex" or (Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*) or (dyslipidemia or dyslipoproteinemia)).ti.	170773
60	exp *Myocardial Infarction/ or exp *heart infarction/ or exp *Heart Failure/ or exp *Pneumonia/ or (("coronary arter*" adj3 occlusion) or (heart adj2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*" or (((heart or cardiac or myocardial) adj2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis") or ("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*")).ti.	716170
61	58 and (59 or 60)	6960
62	limit 61 to yr="2013 -Current"	2705
63	remove duplicates from 62	2017
64	61 not 62	4255
65	remove duplicates from 64	3291
66	63 or 65	5308
67	5 and 66	2924
68	from 67 keep 1-1890	1890
69	from 68 keep 1-1000	1000

70 from 68 keep 1001-1890	890
71 from 67 keep 1950-2924	975
72 from 67 keep 1891-1949	59
73 66 not 67	2384
74 8 and 73	2199
75 from 74 keep 1-1654	1654
76 from 75 keep 1-1000	1000
77 from 75 keep 1001-1654	654
78 from 74 keep 1655-1710	56
79 from 74 keep 1711-2199	489
80 73 not 74	185
81 from 80 keep 1-100	100
82 from 80 keep 111-185	75
83 from 80 keep 101-110	10

Scopus search strategy

1	TITLE(("coronary arter*" W/3 occlusion) or (heart W/2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*") AND TITLE-ABS-KEY(acute)
2	TITLE(((heart or cardiac or myocardial) W/2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis")
3	TITLE("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*")
4	1 or 2 or 3
5	TITLE("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex")
6	TITLE(Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*)
7	TITLE(dyslipidemia or dyslipoproteinemia)
8	5 or 6 or 7
9	TITLE-ABS-KEY(surviv* or death* or mortalit* or fatalit*)
10	LANGUAGE(english)
11	TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (random* W/1 allocat*) or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or

	"case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*))
12	4 and 8 and 9 and 10 and 11
13	TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))
14	12 and not 13
15	DOCTYPE(ab) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
16	14 and not 15
17	PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
18	16 and not 17
19	TITLE(("coronary arter*" W/3 occlusion) or (heart W/2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*") AND TITLE-ABS-KEY(acute)
20	18 and 19
21	TITLE(((heart or cardiac or myocardial) W/2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis")
22	(18 and not 20) and 21
23	18 and not (20 or 22)

SUPPLEMENT TABLE 1

Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for index conditions used in the study.

Diagnosis	*ICD-9-CM* Codes
Acute myocardial infarction	410.00, 410.01, 410.10, 410.11, 410.20, 410.21, 410.30, 410.31, 410.40, 410.41, 410.50, 410.51, 410.60, 410.61, 410.70, 410.71, 410.80, 410.81, 410.90, 410.91
Heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40,

SUPPLEMENT TABLE 2. Characteristics of studies and participants included in meta-analysis

Condition	F/U	Study	Year	Design	N =	Mean age, year	Lipid type	End point	Covariates
AMI	30-day	Cheng et al[1]	2015	observational study	724	68	LDL-C, TG-C	Death	Age, HTN, DM, smoking, family history of CAD, alcohol consumption, ESRD
		Reddy et al[2]	2015	Observational /Registry	115492	67	LDL-C, HDL-C	Death	Age, sex, race, HTN, previous CAD, DM, smoking, blood pressure, heart rate , previous PCI, previous CABG
		Current study	2018	Retrospective cohort	8,696	68	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use
	≥ 2 years	Martin et al[3]	2015	Prospective Substudy	2465	58	RLP-C, IDL-C, VLDL3-C, VLDL-C	Death	Age, sex, race, education, insurance, history of CAD, Dyslipidemia, DM, blood pressure, CKD, HF, CAD, prior PCI, Prior CABG, Smoking, BMI, activity time, alcohol use
		Current study	2018	Retrospective cohort	8,696	68	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use
Heart Failure	≥ 2 years	Afsarmanesh et al[4]	2006	Observational cohort	614	48	TC, LDL-C, HDL-C, TG-C	Death	Sex, age, HF etiology, NYHA, DM, smoking, HTN, BMI, LVEF
		Christ et al[5]	2005	Prospective cohort	422	50	LDL-C	Death	Age, sex, race, education, insurance, history of CAD, dyslipidemia, DM, blood pressure, CKD, HF, CAD, prior PCI, Prior CABG, Smoking, BMI, activity time, alcohol use
		Kahn et al[6]	2013	Observational study	2428	69.8	TC, LDL-C, HDL-C, TG-C	Death	Age, sex, HTN, DM, dyslipidemia, smoking, CKD, Cirrhosis, Statin use, BB use, ACE use, hydralazine use, nitrates use, Digoxin use, lipid level, sodium, hemoglobin, Creatinine, BUN, ALT, AST, albumin
		May et al[7]	2006	Registry	1641	65.5	TC, LDL-C, HDL-C, TG-C	Death	Age, sex, HTN, DM, family history of CAD, smoker, previous CAD, previous CVA, statin use, renal function ,BMI, ejection fraction
		Rauchhaus et al[8]	2003	Prospective cohort	303	62	TC	Death	Age, BMI, sodium, potassium, ESR, TNF, BUN, LVEF, lipid level, NYHA class, Cachexia, medication use (loop diuretic, ACE inhibitor, calcium channel blocker, digoxin, amiodarone, BB, lipid lowering, aspirin)
		Current study	2018	Retrospective cohort	5,758	73	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AMI, acute myocardial infarction; AST, aspartate aminotransferase; BB, beta blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CABG, Coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, Chronic Obstructive Pulmonary Disease; CVA, cerebrovascular accident; DM, Diabetes mellitus; ESRD, end stage renal disease; F/U, follow up; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; HLP, hyperlipidemia; HTN, hypertension; IDL-C, Intermediate-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; N=, number of patients; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RLP-C , remnant-like particles-cholesterol; TC, total cholesterol; TG-C, triglyceride-cholesterol; TNF, tumor necrosis factor; VLDL-C, very-low-density lipoprotein-cholesterol.

References

1. Cheng KH, Chu CS, Lin TH, Lee KT, Sheu SH, Lai WT. Lipid paradox in acute myocardial infarction-the association with 30-day in-hospital mortality. *Crit Care Med.* 2015;43(6):1255-1264.
2. Reddy VS, Bui QT, Jacobs JR, et al. Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). *Am J Cardiol.* 2015;115(5):557-562.
3. Martin SS, Faridi KF, Joshi PH, et al. Remnant Lipoprotein Cholesterol and Mortality After Acute Myocardial Infarction: Further Evidence for a Hypercholesterolemia Paradox From the TRIUMPH Registry. *Clin Cardiol.* 2015;38(11):660-667.
4. Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J.* 2006;152(6):1077-1083.
5. Christ M, Klima T, Grimm W, Mueller HH, Maisch B. Prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy. *Eur Heart J.* 2006;27(6):691-699.
6. Kahn MR, Kosmas CE, Wagman G, et al. Low-density lipoprotein levels in patients with acute heart failure. *Congest Heart Fail.* 2013;19(2):85-91.
7. May HT, Muhlestein JB, Carlquist JF, et al. Relation of serum total cholesterol, C-reactive protein levels, and statin therapy to survival in heart failure. *Am J Cardiol.* 2006;98(5):653-658.
8. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42(11):1933-1940.

SUPPLEMENT TABLE 3. Risk of Bias Assessment (Newcastle-Ottawa Scale)

			Selection				Compatibility		Outcome			
Condition	Study	Year	S1	S2	S3	S4	C1	C2	O1	Q2	O3	Quality
Acute Myocardial Infarction	Cheng et al[1]	2015	*	*	*		*	*	*			6
	Martin et al[2]	2015	*	*	*		*	*	*	*		7
	Reddy et al[3]	2015	*	*	*		*	*	*	*		7
Heart failure	Afsarmanesh et al[4]	2006	*	*	*		*	*	*	*	*	8
	Christ et al[5]	2005		*	*		*		*	*		5
	Kahn et al[6]	2013	*	*	*		*	*	*	*	*	8
	May et al[7]	2006	*	*	*	*	*	*	*	*	*	9
	Rauchhaus et al[8]	2003	*	*	*		*	*	*	*		7

NOTE: S1 = Representativeness of the exposed cohort. S2 = Selection of the non-exposed cohort. S3 = Ascertainment of exposure. S4 = Demonstration that the outcome of interest was not present at the start of the study. C1 = Comparability of the cohort on the basis of design. C2 = Comparability of the cohort on the basis of analysis. O1 = Assessment of outcome. O2 = Was the follow-up long enough for outcomes to occur? O3 = Adequacy of the follow-up of cohorts.

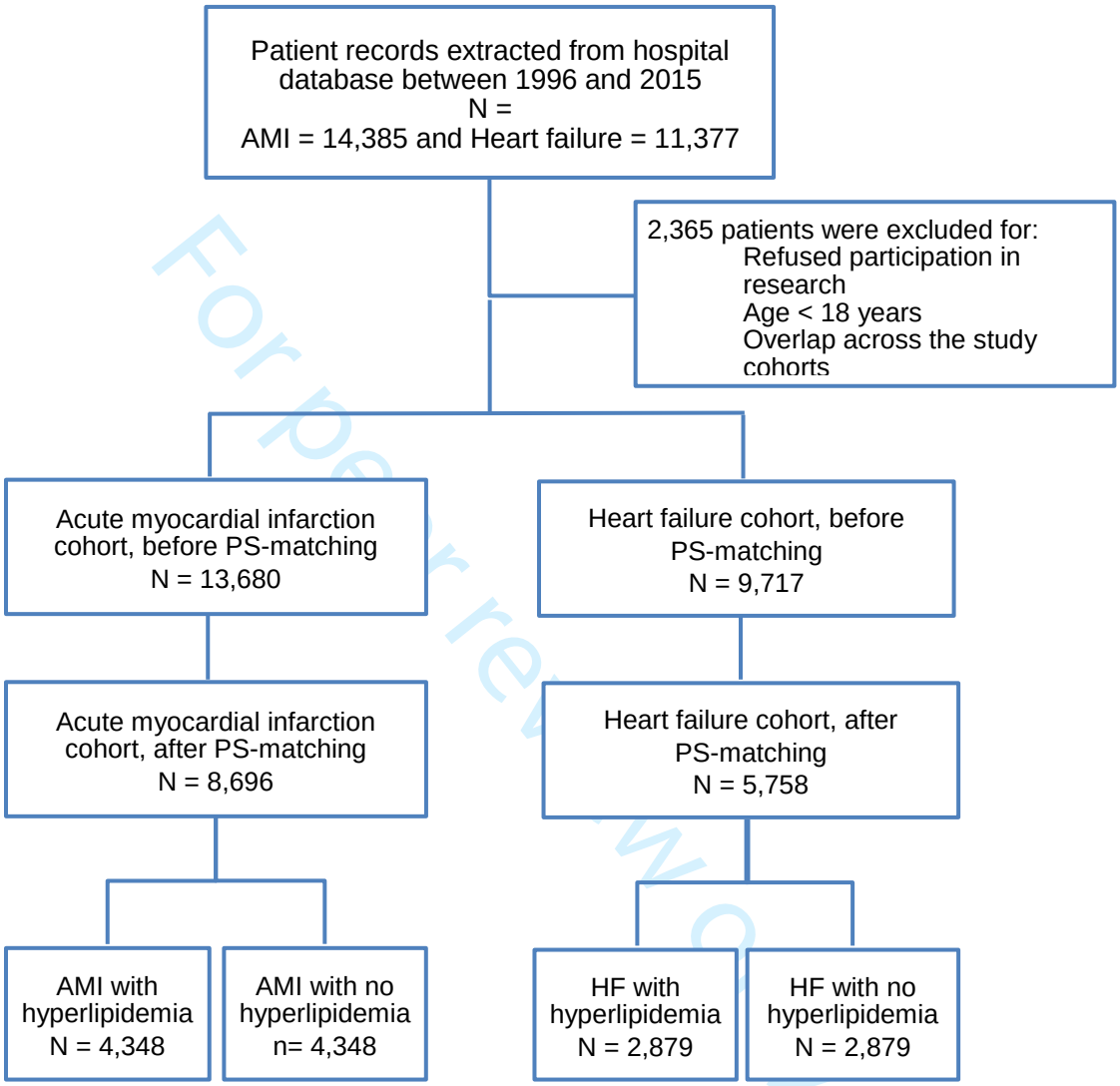
References

1. Cheng KH, Chu CS, Lin TH, Lee KT, Sheu SH, Lai WT. Lipid paradox in acute myocardial infarction-the association with 30-day in-hospital mortality. *Crit Care Med.* 2015;43(6):1255-1264.
2. Reddy VS, Bui QT, Jacobs JR, et al. Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). *Am J Cardiol.* 2015;115(5):557-562.
3. Martin SS, Faridi KF, Joshi PH, et al. Remnant Lipoprotein Cholesterol and Mortality After Acute Myocardial Infarction: Further Evidence for a Hypercholesterolemia Paradox From the TRIUMPH Registry. *Clin Cardiol.* 2015;38(11):660-667.
4. Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J.* 2006;152(6):1077-1083.
5. Christ M, Klima T, Grimm W, Mueller HH, Maisch B. Prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy. *Eur Heart J.* 2006;27(6):691-699.

6. Kahn MR, Kosmas CE, Wagman G, et al. Low-density lipoprotein levels in patients with acute heart failure. *Congest Heart Fail.* 2013;19(2):85-91.
7. May HT, Muhlestein JB, Carlquist JF, et al. Relation of serum total cholesterol, C-reactive protein levels, and statin therapy to survival in heart failure. *Am J Cardiol.* 2006;98(5):653-658.
8. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42(11):1933-1940.

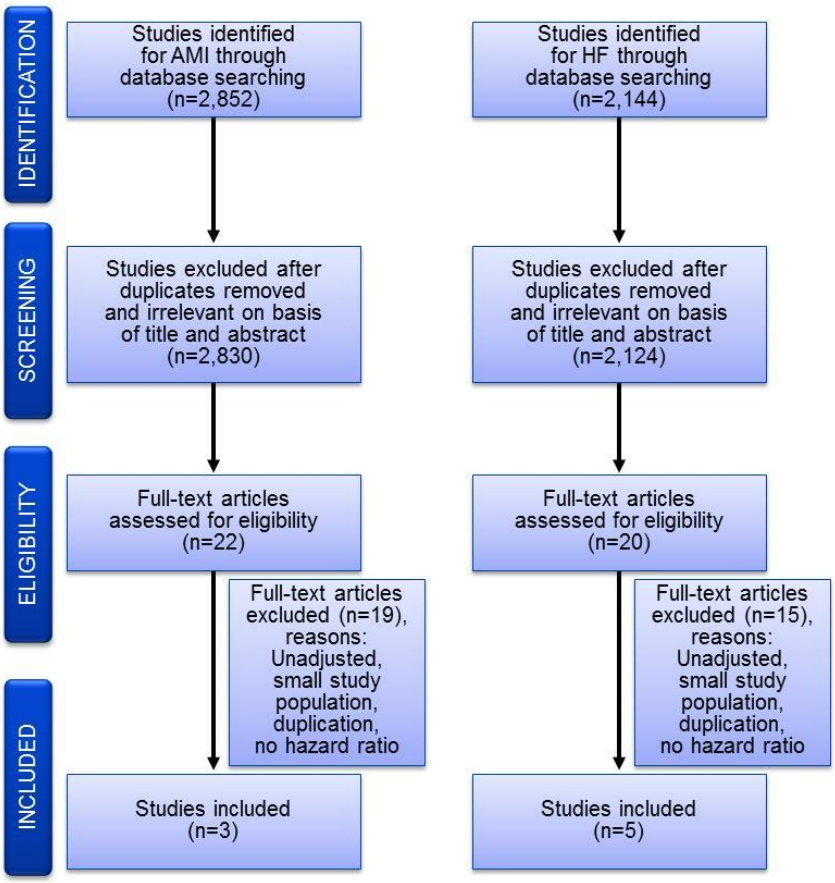
SUPPLEMENT FIGURE 1

Flow diagram. **STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram of the process of selection of study cohorts from Mayo Clinic Hospital Data Base**



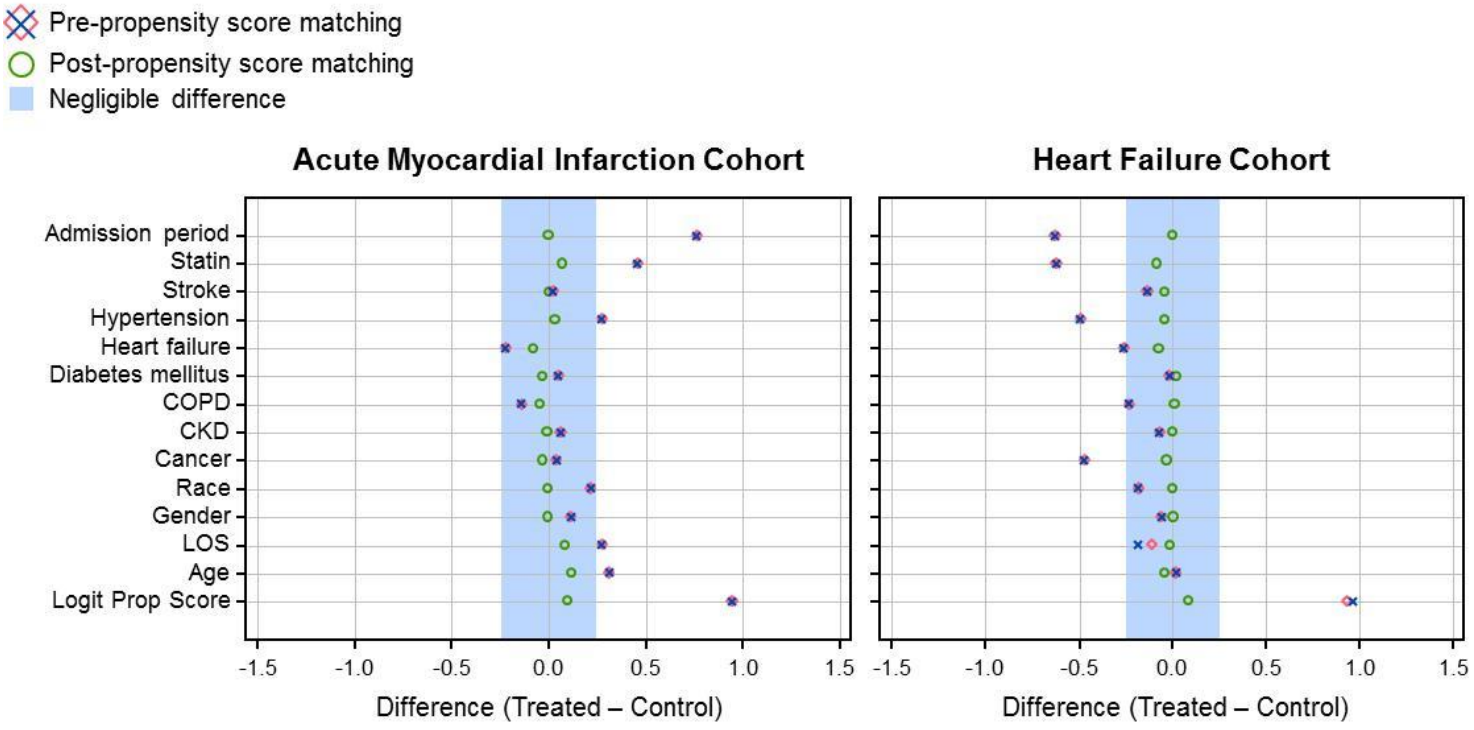
SUPPLEMENT FIGURE 2

PRISMA flow diagram of evidence search and selection of studies for meta-analysis



SUPPLEMENT FIGURE 3

Love plot showing standardized differences for baseline covariates comparing original propensity-score unmatched to propensity-score matched samples, acute myocardial infarction cohort (left panel) and heart failure cohort (right panel)



Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LOS, length of hospital stay

BMJ Open

Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Acute myocardial infarction, Heart failure < CARDIOLOGY, Hyperlipidemia, Mortality, Adult cardiology < CARDIOLOGY

Title:

Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

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Key words: hyperlipidemia, mortality, acute myocardial infarction, heart failure

Word count:

Abstract	299
Text	3,954
Tables	2
Figures	3
References	61

ABSTRACT

Objective To examine the effect of hyperlipidemia (HLP), defined as having a preexisting or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥100 mg/dl during index hospitalization or within the preceding 6 months, on all-cause mortality after hospitalization for acute myocardial infarction (AMI) or acute decompensated heart failure (ADHF) and to determine whether HLP modifies mortality associations of other competing comorbidities. A systematic review and meta-analysis to place the current findings in the context of published literature.

Design Retrospective study, 1:1 propensity-score matching cohorts; a meta-analysis.

Setting Large academic center, 1996 to 2015

Participants Hospitalized patients with AMI or ADHF

Main outcomes and measures All-cause mortality and meta-analysis of relative risks (RR).

Results: Unmatched cohorts: 13,680 patients with AMI (age [mean] 68.5 ± [SD] 13.7 years; 7,894 [58%] with HLP) and 9,717 patients with ADHF (age, 73.1 ± 13.7 years; 3,668 [38%] with HLP). In matched cohorts, the mortality was lower in AMI patients (n = 4,348 pairs) with HLP vs no HLP, 5.9 vs 8.6/100 person-years of follow up, respectively (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.72 – 0.80). A similar mortality reduction occurred in matched ADHF patients (n = 2,879 pairs) with or without HLP (12.4 vs 16.3 deaths/100 person-years; HR 0.80, 95% CI 0.75 – 0.86). HRs showed modest reductions when HLP occurred concurrently with other comorbidities. Meta-analyses of 9 observational studies showed that HLP was associated with a lower mortality after incident AMI or ADHF (AMI: RR 0.72, 95% CI 0.69 – 0.76; HF: RR 0.67, 95% CI 0.55 – 0.81)

Conclusions: Among matched AMI and ADHF cohorts, concurrent HLP, compared with no HLP, was associated with a lower mortality and attenuation of mortality associations with other competing comorbidities. These findings were supported by a systematic review and meta-analysis.

Strengths and limitations of this study

- Cohort study comprised of patients with cardiologist-confirmed diagnoses, high rates of case ascertainments, and prompt mortality updates. Meta-analysis portion of the study adhered to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) Protocols.
- Large sample size and event rates (AMI, n = 8,696, deaths 4,900; HF, n = 8,758, deaths 3,635) and longer-term follow up (median follow-up in years: AMI, 8.8; HF, 6.3) allowed detailed assessment of the association of hyperlipidemia with mortality across multiple categories.
- 1:1 propensity score-matched pairs of patients with acute myocardial infarction or acute decompensated heart failure to balance the differences in baseline variables between patients who have concurrent hyperlipidemia and those who did not.
- Limitations of the study include inherent disadvantages of retrospective cohort studies, potential unmeasured confounders, *International Classification of Diseases, Ninth Revision, Clinical Modification* to identify study cohorts, ascertainment of comorbid conditions during index hospitalization and lack of data on subsequent acquisition of these conditions during the follow-up.

Introduction

Early epidemiological studies of 1970s and 1980s including Framingham Heart Study(1), Multiple Risk Factor Intervention Trial (MRFIT)(2), Coronary Primary Prevention Study(3), and Helsinki Heart Study(4), all provided substantial evidence for the epidemiological relationship between cholesterol levels and incident coronary artery disease in general population. In 2007, a meta-analysis of individual data from

61 prospective studies suggested that total cholesterol was positively associated with cardiovascular mortality(5). However, contemporary studies largely examined the effect of statins and other cholesterol lowering interventions on cardiovascular events (6, 7). A similar relationship between hyperlipidemia (HLP) and incident heart failure (HF) has been reported (6-9). Surprisingly, several recent studies found an inverse association wherein HLP, counterintuitively, conferred an overall survival benefit in patients with established acute myocardial infarction (AMI)(10-13) and HF(14). Although cholesterol levels in general population predict new cardiovascular events, it is unclear whether a positive association persists after incident AMI or HF. Furthermore, the effect of HLP on the association of other competing conditions with mortality is unknown.

Systematic reviews and meta-analyses on the association of HLP with new AMI have already been published(5), but, the clinical trials evaluating this relationship after the incident AMI have not been systematically reviewed. Additionally, the data are limited on the association between HLP and incident HF and subsequent mortality. A comprehensive review of published data on the association of HLP with mortality after incident AMI or HF would clarify these issues.

We postulated that if a diagnosis of HLP decreases the mortality after AMI or HF, then, it also lessens the magnitude of mortality risks associated with other competing comorbidities. We tested this hypothesis, separately, in large cohorts of patients hospitalized for incident AMI and acute decompensated HF (ADHF). To compare patients with and with no HLP, we assembled 1:1 balanced groups using propensity score-matching for each study condition. Our objectives were three-fold: 1) to estimate the association of HLP with all-cause mortality among patients with AMI or ADHF, 2) to determine the extent to which the association between other competing comorbidities(15) and mortality is modified by HLP 3) and to provide risk estimates for mortality associated with HLP after incident AMI or HF through systematic

review and meta-analyses of published and current study data to place the current findings in the context of published literature.

Methods

Cohort study

STUDY POPULATION AND DATA COLLECTION

The study cohorts were comprised of adults aged ≥18 years, hospitalized at Mayo Clinic from August 1, 1996 to September 17, 2015 with primary discharge diagnoses of AMI or acute decompensated HF (ADHF) with follow up completed through August 17, 2016. AMI included both ST-elevation myocardial infarction (STEMI) and non-STEMI. ADHF comprised of heart failure with both reduced and preserved ejection fractions. Discharge diagnoses were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (presented in supplement table 1). Mayo clinic has one of the oldest and most advanced medical record systems in the United States. Patient provided information is constantly updated at every clinic or hospital visit at its main Rochester campus and at a network of clinics and hospitals across more than 60 communities in states of Iowa, Wisconsin, and Minnesota. The STROBE flow diagram of study cohorts selection of is presented in supplement figure 1. Further details of data extraction are published elsewhere(16). The study was approved by the Mayo Clinic Institutional Review Board and need for patient consent was waived.

ASCERTAINMENT OF ACUTE MYOCARDIAL INFARCTION AND ACUTE DECOMPENSATED HEART FAILURE

For each patient the primary discharge diagnosis, AMI or ADHF, was documented by the attending physician at the time of discharge, assigned ICD-9-CM code, and subsequently captured by the abstractors.

ASCERTAINMENT OF COMORBID CONDITIONS

We focused on a panel of 20 comorbid conditions (CCs) defined by Department of Health and Human Services (15) and identified by Clinical Classifications Software codes of US Healthcare Cost Utilization

Project. CCs with prevalence < 3% were excluded from analysis. To ascertain the comorbid effect of HLP on other concurrent condition, we paired HLP with each other competing comorbidity within an individual patient.

ASCERTAINMENT OF HYPERLIPIDEMIA AND STATIN USE

HLP was defined as having a preexisting or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥100 mg/dl as clinically measured during index hospitalization or within the preceding 6-months. LDL-C was measured indirectly by Friedewald method(17). Published reports suggest that lipid panel measured during the first 24 hours after an acute cardiovascular event reliably represents baseline level(18). Statin use was based on discharge medication reconciliation.

ASCERTAINMENT OF MORTALITY

All deaths occurring from admission to censoring date of August 17, 2016 were abstracted from medical records. The mortality data is updated regardless of the cause of death, including death due to murders, suicides, or accidents. At the time of drafting the manuscript, Minnesota all-cause (including suicide, murder, misadventures, and natural) Electronic Death Certificate Data is current to December 31, 2018,

PATIENT FOLLOW-UP

All patients were followed from index hospitalization until death or censoring date of August 17, 2016 whichever occurred first.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in this study

Systematic review and meta-analysis

DATA SOURCE AND SEARCHES

This systematic review and meta-analysis was conducted in accordance with the established methods(19) and followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines(20). We searched of MEDLINE, EMBASE, Cochrane Library, Web of Science

databases for eligible trials from inception through September 2017 with continued surveillance through February 2018 for trials examining the associations of HLP with mortality. We identified clinical studies with the same PICO (population, condition/disease, intervention, control and at least one outcome) and objectives. Studies with incomplete data were excluded. Methodological details of the meta-analysis are published elsewhere(21). The search strategy is presented in the supplement.

STUDY SELECTION

Eligibility criteria included: (1) randomized or non-randomized clinical trials of adults with AMI or HF (2) comparator groups HLP or hypercholesterolemia vs HLP or hypercholesterolemia as defined by individual study investigators, and (3) mortality as the primary outcome or one of the outcomes.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

From the results of initial search, two investigators (EA and HA), working independently reviewed articles for eligibility on the basis of titles and abstracts. Studies that satisfied the inclusion and exclusion criteria were retrieved for full text review. Disagreements were resolved by consensus and retained conflicts were adjudicated by a third investigator (MY). We extracted the following data from each study: type of study, number of participants, age, gender, presence and absence of hyperlipidemia, length of follow-up, and outcome measures. Measure of association with clinical outcomes (hazard ratio [HR], odds ratio [OR], or relative risk [RR]) were abstracted. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies(22).

Statistical analysis

ALL Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA)

1. THE COHORT STUDY

Propensity score analysis(23): We assembled 1:1 propensity score-matched pairs of patients with AMI or ADHF to balance the differences in baseline variables between patients with and without concurrent

HLP. Propensity scores were estimated using logistic regression (PROC PS MATCH in SAS) based on age, gender, length of stay, race, comorbidities, statin prescription on discharge, and time period (1996-2005 vs. 2006-2016). Standardized differences in the matched cohort ranged from 0.122 to 0.004. One-to-one nearest neighbor caliper matching was used to match patients based on the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score. Patients were of exact match on gender, race and enrollment period. Patients without HLP were matched to one with HLP generating a quasi-randomized design whereby study groups (HLP vs no HLP) have had similar propensity for allocation to either group.

Kaplan-Meier estimates: Kaplan-Meier estimates were performed using propensity-score matched cohorts and stratified log-rank tests were used to compare survival curves.

Multivariable Cox models: Cox proportional hazards models were performed on the matched samples using a robust variance estimator to account for matching. Multiple models were constructed for estimating hazard ratios (HR) for mortality. Model 1 estimated HR and 95% confidence intervals (CI) for mortality associated with HLP and other CCs. Model 2 was extended to fit Model 1 plus statin therapy. Model 3 examined the comorbid effect of HLP in combination with other competing comorbidities.

Sensitivity analysis: We performed several sensitivity analyses to ascertain the degree of bias that might explain significant associations between HLP and mortality and to confirm the robustness of our findings. From propensity-score matched AMI and HF patients we identified patients with available data related to BMI, LDL-C, left ventricular ejection fraction (LVEF), and serum concentrations of sodium blood urea nitrogen (BUN), and creatinine. We conducted sensitivity analyses using separate Cox proportional regression models by excluding 1) patients with no LDL-C data, 2) patients with no available data on levels of sodium, blood urea nitrogen (BUN), and creatinine, 3) patients with no available data on body mass index (BMI) 4) patients with no available data on left ventricular ejection fraction (LVEF).

2. THE META-ANALYSIS

The DerSimonian and Laird random-effects model was used to pool estimates across studies (24). The results were expressed as relative risk (RR) and 95% CI. Heterogeneity was assessed using I^2 to reflect proportion of heterogeneity not attributable to chance(25). The number of studies was insufficient to statistically evaluate publication bias. Characteristics of included studies (Supplement table 2), assessment of risk of bias (supplement table 3), and PRISMA flow diagram (Supplement figure 2) are presented in supplement.

Results

1. THE COHORT STUDY

Cohort study population

The supplemental Figure 1 illustrates the Strengthening the Reporting of Observational Studies in Epidemiology flow diagram for selection of final study cohorts: AMI (Initial cohort n = 13,680; propensity score-matched cohort n = 8,696 , pairs 4,348) and ADHF (Initial cohort n = 9,717; propensity score-matched cohort n = 5,758, pairs 2,879).

Baseline characteristics

Baseline characteristics for each study cohort, before and after propensity score-matching by HLP are presented in Table 1. Baseline characteristics for matched patients in each cohort were balanced. Before matching patients with HLP were younger, more likely to be males, and had lower rates of COPD and HF and high prevalence of chronic kidney disease (CKD) and hypertension in the AMI cohort. As these variables were balanced in propensity score-matching, a balanced cohort with standardized differences of <10% for baseline characteristics was created for final analysis. Supplement figure 3

illustrates a love plot of standardized differences before and after propensity-score matching to allow visualization of improvement in prognostic balance. Of 20 CCs, only 8 were included in final analysis for their frequency ≥3%.

MORTALITY

Acute myocardial infarction: In matched patients, mortality was significantly lower among patients with HLP vs those with no HLP (overall mortality 2,182 [50.2%] vs 2,718 [62.5%] or 5.9 vs 8.6 deaths/100 person-years of follow up, P <0.0001). Median and person-years of follow up was greater in matched patients with HLP (median 8.8 years, interquartile [IQ] 3.2 – 13.1 years, 37,068 person-years of follow-up) vs those with no HLP (median 6.3 years, IQ 1.4– 12.4 years, 31,569 person-years of follow-up).

Acute decompensated heart failure: In matched patients, mortality was significantly lower among patients with HLP vs those with no HLP (overall mortality 1,687 [58.6%] vs 1,948 [67.7%] or 12.4 vs 16.3 deaths/100 person-years of follow-up, p <0.0001). Median and person-years of follow up was greater in matched patients with HLP (Follow up: median 3.2 years, IQ 1.0 – 6.9 years, 13,577 person-years of follow-up) vs those with no HLP (median 2.5 years, IQ 0.7 – 6.2 years, 11,951 person-years of follow-up).

KAPLAN-MEIER ESTIMATES

Figure 1 displays Kaplan-Meier estimates of all-cause mortality by HLP in propensity-score matched samples of AMI or ADHF patients. Kaplan-Meier survival curves diverged immediately after hospitalization and then remained parallel during the follow-up in both AMI or ADHF cohorts. Log-rank *P* value for patients with and with no HLP remained < 0.0001 for each index condition. In multiple sub-analyses, risk differences in mortality between patients with and without HLP persisted in age <65 and ≥65 years, male and female, white and non-White with log-rank p <0.0001 for all sub-groups.

COX PROPORTIONAL REGRESSION MODEL 1

The results are presented in Figure 2. HLP as compared with no HLP, was associated with a lower risk of death from any cause after AMI (HR 0.76, 95% confidence interval [CI] 0.72 – 0.80, n = 8,696) or ADHF (HR 0.80, 95% CI 0.75 – 0.86, n = 5,758). Findings did not change significantly with exclusion of patients with a new in-hospital HLP diagnosis in sensitivity analysis. Co-occurrence of cancer, CKD, COPD, diabetes mellitus, HF, or stroke independently increased mortality following AMI or ADHF. While hypertension reduced mortality by 8% (95% CI 0.87 – 0.98) after AMI, neither hypertension nor CAD influenced mortality after ADHF hospitalization.

COX PROPORTIONAL REGRESSION MODEL 2

In separate analysis, adjustment of Cox proportional model for statin treatment did not change results for baseline HLP in predicting the all-cause mortality (AMI: HR 0.69, 95% CI 0.65 - 0.73; ADHF: HR 0.78, 95% CI 0.73-0.83).

COX PROPORTIONAL REGRESSION MODEL 3

The results of Cox model 3 are shown in Figure 2. Magnitude of HRs for mortality associated with cancer, COPD, CKD, diabetes, heart failure, and stroke were all modestly attenuated with concurrent HLP across study cohorts. By comparison, protective effect of HLP on mortality was enhanced when paired with HTN in both AMI (HR 0.77, 95% CI 0.72- 0.83) and ADHF (HR 0.86, 95% CI 0.78-0.94).

SENSITIVITY ANALYSIS WITH AVAILABLE DATA ON FOLLOWING COVARIATES

1. *BMI*: Of 8,646 patients with AMI 6,092, and of 5,758 patients with HF, 5,311 have data for BMI. The association of HLP with mortality remained unchanged when multivariable model accounted for BMI. BMI was inversely related to mortality with 1 unit increase in BMI resulting in 1% reduction in mortality in both AMI (HR 0.99, 95% CI 0.98 – 0.99, P = 0.0130) and HF (HR 0.99, 95% CI 0.98 – 0.99, P <0.0001) cohorts (table 2)

2. *LDL-C on or within 6-months preceding admission:* Overall, 7,268 patients (84%) in AMI cohort and 4,562 patients (79%) in HF cohort had LDL-C clinically measured on or within 6-month preceding hospitalization. We stratified patients into quartiles according to levels of LDL-C, <70 mg/dl, 70 – 99 mg/dl, 100 – 129 mg/dl, and ≥ 130 mg/dl. There was a graded reduction in mortality from highest to the lowest LDL-C quartile in both AMI and HF (table 2).
3. *Levels of sodium, BUN, and creatinine.* AMI: 7,603 (87%), 6609 (70%), and 7,812 (90%) had data available on sodium, BUN, and creatinine respectively. HLP remained an independent predictor of lower mortality compared to no HLP when accounted for levels of sodium (≤ 135 vs >135 mmol/l), BUN (≤ 19 vs >19), and creatinine (≤ 1.5 vs >1.5) (Table 2). HF: 7,603 (87%), 6609 (70%), and 7,812 (90%) had data available on sodium, BUN, and creatinine respectively. HLP remains an independent predictor of lower mortality compared to no HLP when accounted for levels of sodium (≤ 135 vs >135 mmol/l), BUN (≤ 19 vs >19), and creatinine (≤ 1.5 vs >1.5) (Table 2).
4. *LVEF:* A total of 5,408 patients (62%) with AMI and 3,869 patients (67%) patients with ADHF had data available on LVEF, measured clinically during or within 6 months preceding hospitalization. HLP remained an independent predictor of lower mortality compared to no HLP when adjusted for LVEF in AMI and ADHF (Table 2).

2. <u>META-ANALYSIS</u>

Hyperlipidemia was associated with lower all-cause mortality after AMI (30-day mortality: 3 studies(10, 26), n = 124,912, RR 0.66, 95% CI 0.45 – 0.97; long-term mortality [≥ 2 years]: 2 studies(27), n = 11,161, RR 0.72, 95% CI 0.69-0.76) and ADHF (long-term mortality [≥ 2 years]: 6 studies(28-32), n = 11,166, RR 0.67, 95% CI 0.55 – 0.81). Meta-analysis of AMI was homogenous (I^2 0%) however, substantial heterogeneity was noted in heart failure meta-analysis reflecting different settings in the observational studies. The results of meta-analysis are presented as forest plots (Figure 3).

Discussion

MAIN FINDINGS

This propensity-score matched study of large cohorts of patients hospitalized for AMI or ADHF and a systematic review with meta-analysis provided a rigorous assessment of the association between HLP and long-term all-cause mortality. First, a diagnosis of HLP, compared to no HLP, was associated with 24% and 20% relative risk reduction in all-cause mortality corresponding to 27 and 39 fewer deaths per 1000 person-years after incident AMI and ADHF, respectively. The reduced mortality associated with HLP was robust to adjustment for potential confounder including demographics, clinical characteristics, and key CCs. The association was consistent across the following subsets: young and old, male and female, white and non-white, and prevailed across both study cohorts. The reductions in mortality were independent of benefit attributable to statin therapy. Kaplan-Meier estimates suggest that the reduction in cumulative incidence of death from HLP begins immediately after hospitalization and is maintained into follow-up both in AMI and HF cohorts. Second, we found that cancer, COPD, CKD, diabetes mellitus, heart failure, or stroke, were all significantly associated with increased long-term mortality. This increased risk was offset by the lower mortality from HLP resulting in attenuation or even a null effect on mortality in patients with AMI or ADHF who had HLP concurrent with other CCs. By comparison, hypertension while having no effect in HF, was inversely associated with mortality in AMI, similar to HLP. The magnitude of mortality reduction associated HLP was enhanced in the presence of HTN after incident AMI and ADHF. Third, the complementary meta-analysis of published observational studies and current study data demonstrated consistent results and provide further evidence that HLP is associated with decreased mortality following incident AMI or ADHF. Multiple sensitivity analyses among patients with available data on BMI, LDL-C, LVEF, levels of sodium, BUN, and

creatinine were all yielded similar results and the association between HLP and mortality remained robust in AMI and ADHF.

COMPARITVE STUDIES

The association of hyperlipidemia with atherosclerotic cardiovascular disease is largely based on epidemiological studies (1-4) and randomized clinical trials of LDL-C lowering therapy. These studies have important limitations and do not ascertain causal relationship. Although genetic studies are promising and have the potential to address causal relationship of LDL-C with atherosclerotic cardiovascular disease(33), the co-inheritance of other pro-atherogenic factors that affect atherosclerotic cardiovascular disease may not be determined(34). Findings of this study dispute general assumption that hyperlipidemia is associated with increased mortality. However, several community- and hospital-based population studies contradict this notion and support our findings. A number of large community-based population studies from Scandinavian countries showed that hyperlipidemia is inversely related to mortality, particularly in older adults (35-38). These observations were reproduced in large community-based prospective cohort studies from Japan(39). A prospective observational study found that low LDL-C on admission was associated with a lower 3-year survival after hospitalization for non-ST elevation myocardial infarction(40). An earlier systematic review found that the mortality risk from HLP decreased with increasing age(5). By comparison, we found that HLP maintained its survival benefit even in older adults, a finding supported by a meta-analysis of 19 cohort studies that showed inverse association between elevated cholesterol and mortality(41). These observations were reinforced by widely used risk-prediction models for AMI and HF in which HLP did not make into the final prediction models (12, 13, 42-44) suggesting a weaker or no association with mortality. An inverse relationship between HLP and mortality was reported for a number of other conditions not the focus of this study(45-47). Similarly, numerous other conditions such hypertension, cigarette smoking, and factor V Leiden exhibit epidemiological paradox(48-50). According to

epidemiologists, these paradoxes may exemplify collider or index event bias wherein established risk factor for first occurrence of a disease becomes inversely related after the occurrence of an event (51-53). The effect of HLP might be concealed in the presence of stronger competing risk factors for mortality (54). Other potential mechanisms include a progressive increase in proportion of deaths from non-cardiovascular conditions with differential association with baseline cholesterol (55) and a reverse causation, whereby underlying disease lowers the cholesterol level and increases the risk of death. Numerous investigators argued that low cholesterol represents a biological marker for concurrent cachexia, malnutrition, cancer, and other chronic diseases with proven adverse impact on survival (56, 57). However, HLP remained a predictor of lower mortality in several studies that even excluded terminal diseases (41). Our results support the concept of obesity paradox among patients with HF and AMI and findings were consistent with several published studies. Previous studies reported that even healthy subjects with low cholesterol are especially predisposed to infectious diseases (58-60). Although our findings were adjusted for cancer and numerous other CCs, the potential confounding by undiagnosed cachexia or malnutrition cannot be excluded. Our findings were contradicted by a number of randomized clinical trials and meta-analyses of statin therapy in AMI that demonstrated a dose dependent decrease in the risk of cardiovascular events with reduction in LDL-C level, even down to <70 mg/dl(6). These discrepant findings are attributable to demographic differences, patient population with lower rates of CCs, shorter follow-up intervals, and focus on cardiovascular events including cardiovascular mortality rather than all-cause mortality as the outcome.

CLINCAL IMPLICATIONS

The findings of this study, if validated, should reinforce the importance of HLP in predicting long-term mortality after index AMI or ADHF and potentially provide guidance for subsequent management. HLP can readily be diagnosed and help recognize AMI and HF patients with lower long-term mortality. In

these patients, clinical care should not focus on certain lipid targets; rather evidence-based secondary prevention strategies should be initiated. Conversely, patients with AMI and ADHF without HLP may be considered to have increased risk for early mortality and potentially alert providers for close monitoring during hospitalization and after discharge. Both categories of patients would profit from thoughtful tailored programs with distinctive goals of care for existing CCs.

STRENGTHS AND LIMITATIONS

This study has several strengths. Firstly, large study cohorts, high level of case ascertainment for incident events and prompt mortality update(61) allowed precise estimation of mortality risks. Broader range of patient population, long follow-up extending to 20 years, and all-cause rather than cardiovascular mortality as the primary outcome are additional advantages over randomized controlled trials. Secondly, propensity-score matching to balance observed patient-characteristics enabled further control of potential differences. Thirdly, we conducted a systematic review and meta-analysis to place the findings of this study in the larger context of existing literature with consistent findings. The study also has a number of important limitations. These included possibility of unmeasured confounders, reliance on ICD-9-CM codes to identify study cohort, Clinical Classifications Software codes to assess coexisting CCs, ascertainment of CCs during index hospitalization, and lack of data on subsequent acquisition of these conditions during the follow up. Our study cohorts were homogenous with respect to race and substantially older than those observed in most clinical trials, but, similar to those in many epidemiological studies. The pre-existing hyperlipidemia and CCs were physician-diagnosed during index hospitalization rather than being assigned by study investigators. Meta-analysis of ADHF was associated with heterogeneity; nevertheless, the results from all the included studies suggested a reduction in mortality with HLP. Despite some limitations, the findings of the present study may be extended to hospital-based, AMI and ADHF population at large.

CONCLUSIONS

The current findings, based on large unselected hospital-based patient-populations, provide strong evidence that after incident AMI or ADHF, a diagnosis of HLP, compared to no HLP, was associated with reduced long-term mortality, a longer median survival, and modest attenuation of the magnitude of mortality risk associated with other competing CCs. Our data support a protective role for HLP against all-cause mortality following incident AMI and ADHF. Further studies are needed to understand the complex relationship between HLP and mortality, especially in the presence of other competing comorbidities and to define appropriate HLP targets to maximize the benefits.

Footnotes

Contributors MY, PT, KJ, EM, JS, TD, ZW, VS, and MM contributed to the initial conception of the study. MY, PT, BM, EM, HA, JS, TD, KJ, US, ZW, VS, and MM made substantial contributions to the statistical methodology, analysis and data interpretation. MY, JS, TD, KJ LM wrote the first draft of the manuscript. MY, PT, BM, EM, HA, JS, TD, KJ, US, ZW, VS, and MM provided substantial revisions to the manuscript. All authors approved the final version of the protocol.

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Table 1. Patient characteristics and standardized differences before and after propensity score-matching

Variables		All Patients (n=13,680)			Propensity score-matched cohort (n=8,696)		
		With hyperlipidemia n=8,929	With no hyperlipidemia n=4,751	Absolute Standardized Difference	With hyperlipidemia n=4,348	With no hyperlipidemia n=4,348	Absolute Standardized Difference
Acute myocardial infarction							
Demographics	Age, y, mean ± SD	67.0 ± 13.6	71.3 ± 13.5	0.315	68.9 ± 13.3	70.6 ± 13.6	0.122
	Male n = (%)	6,035 (68)	2,938 (62)	0.121	2,761 (64)	2,761 (64)	0
	White n= (%)	8,108 (91)	3,963 (83)	0.222	3,744 (86)	3,744 (86)	0
Anthropometric measurements	BMI kg/m^2	30.1 ± 6.2	28.8 ± 6.3	-	29.8 ± 6.3	28.9 ± 6.3	-
	BMI, missing n = (%)	1,556 (17)	1,520 (32)	-	1,274 (29)	1,330 (31)	-
Clinical characteristics	LOS, days, median (quartiles 25%-75%)	3 (2-5)	4 (3-8)	0.275	4 (3-6)	4 (3-7)	0.086
Year of hospital admission	1996-2005 n = (%) 2006-2016 n = (%)	3886 (44) 5043 (57)	3732 (79) 1019 (21)	0.770	3341 (77) 1007 (23)	3341 (77) 1007 (23)	0
Comorbid conditions	CAD, n = (%)	-	-		-	-	
	Cancer, n = (%)	744 (8)	342 (7)	0.042	279 (6)	313 (7)	0.029
	CKD, n = (%)	885 (12)	380 (8)	0.067	348 (18)	353 (8)	0.004
	COPD, n = (%)	820 (9)	640 (14)	0.136	482 (11)	543 (13)	0.044
	Diabetes, n = (%)	2,567 (29)	1,249 (26)	0.055	1,091 (295)	1,149 (26)	0.030
	Heart failure, n = (%)	1,762 (20)	1,376 (29)	0.216	1,033 (24)	1,173 (27)	0.075
	Hypertension, n = (%)	6,049 (68)	2,584 (54)	0.277	2,530 (58)	2,453 (56)	0.037
	Stroke, n = (%)	359 (4)	168 (4)	0.025	151 (4)	148 (3)	0.004
Lipid levels	LDL-C mg/dl	110.9 ± 39.2	78.7 ± 25.0	-	118.4 ± 37.6	78.8 ± 25.1	-
	LDL-C, missing n = (%)	483 (5)	1,356 (29)	-	251 (6)	1,177 (27)	-
Drug treatment	Statin	4,665 (52)	1,431 (30)	0.461	1,566 (36)	1,412 (33)	0.074
Heart Failure							

Variables		All Patients (n=9,717) With hyperlipidemia n=3,941	All Patients (n=9,717) With no hyperlipidemia n=5,776	All Patients (n=9,717) Absolute Standardized Difference	Propensity score-matched cohort (n=5,758) With hyperlipidemia n=2,879	Propensity score-matched cohort (n=5,758) With no hyperlipidemia n=2,879	Propensity score-matched cohort (n=5,758) Absolute Standardized Difference
Demographics	Age, y, mean ± SD	73.2 ± 12.4	73.0 ± 14.5	0.020	72.6 ± 12.6	73.1 ± 14.1	0.040
	Male n = (%)	2,342 (59)	3,266 (57)	0.058	1,682 (54)	1,682 (54)	0
	White n = (%)	3,574 (91)	4,896 (85)	0.181	2,588 (90)	2,588 (90)	0
Anthropometric measurements	BMI kg/m^2	31.1 ± 7.6	29.7 ± 7.5	-	31.0 ± 7.6	30.0 ± 7.5	-
	BMI, missing n = (%)	193 (5)	780 (13)	-	185 (6)	262 (9)	-
Clinical characteristics	LOS, days, median (quartiles 25%-75%)	4 (2 – 6)	4 (2 – 7)	0.183	4 (2 – 6)	4 (2 – 7)	0.018
Year of hospital admission	1996-2005 n = (%) 2006-2016 n = (%)	1221 (31) 2720 (69)	3510 (61) 2266 (39)	0.626	1197 (42) 1682 (58)	1197 (42) 1682 (58)	0
Comorbid conditions	CAD, n = (%)	2,482 (63)	2,309 (40)	0.472	1,580 (55)	1,537 (53)	0.031
	Cancer, n = (%)	595 (15)	736 (13)	0.068	419 (15)	420 (15)	0.001
	CKD, n = (%)	1,286 (33)	1,299 (23)	0.228	802 (28)	819 (28)	0.013
	COPD, n = (%)	813 (21)	1,152 (20)	0.017	567 (20)	584 (20)	0.015
	Diabetes, n = (%)	1,617 (41)	1,660 (29)	0.260	1,117 (39)	1,015 (35)	0.075
	Heart failure, n = (%)	-	-	-	-	-	-
	Hypertension, n = (%)	2,911 (74)	2,930 (51)	0.492	1,931 (67)	1,869 (65)	0.046
	Stroke, n = (%)	160 (4)	106 (2)	0.132	94 (3)	75 (3)	0.039
Lipid levels	LDL-C mg/dl	92.8 ± 39.9	75.5 ± 28.5	-	98.5 ± 41.0	74.0 ± 28.5	-
	LDL-C, missing n = (%)	517 (13)	2,130 (37)	-	268 (13)	928 (32)	-
Drug treatment	Statin	1731 (44)	963 (17)	0.621	906 (32)	800 (28)	0.084

Table 2. Results of 4 sensitivity analysis by separate Cox proportional regression models among patients with acute myocardial infarction or heart failure in whom the relevant data point were available. Model 1, propensity-score matched patients with available data on BMI; Model 2, propensity-score matched patients with available data on LVEF; Model 3, propensity-score matched patients with available data on LDL-C measured on admission or within the preceding 6 –months; Model 4, propensity-score matched patients with available data on sodium, BUN, and creatinine levels measured on admission.

Acute myocardial infarction

Variables	Model 1 HR (95% CI) P value	Model 2 HR (95% CI) P value	Model 3 HR (95% CI) P value	Model 4 HR (95% CI) P value
Age	1.06 (1.05 – 1.06) <0.0001	1.07 (1.06 – 1.07) <0.0001	1.06 (1.05 – 1.06) <0.0001	1.06 (1.05 – 1.06) <0.0001
Gender	1.06 (0.99 – 1.14) 0.1123	1.04 (0.96 – 1.13) 0.3128	1.07 (0.99 – 1.14) 0.0650	1.07 (0.96 – 1.11) 0.3931
Ethnicity	0.79 (0.71 – 0.89) 0.0001	0.76 (0.65 – 0.89) 0.0006	0.735 (0.67 – 0.87) 0.9286	0.83 (0.75 – 0.92) 0.0003
Length of stay	1.01 (1.01 – 1.02) <0.0001	1.01 (1.01 – 1.02) <0.0001	1.02 (1.01 – 1.02) <0.0001	1.00 (0.99 – 1.01) 0.1374
Cancer vs no cancer	1.82 (1.62 – 2.05) <0.0001	2.08 (1.82 – 2.39) <0.0001	1.77 (1.57 – 1.99) <0.0001	1.76 (1.56 – 1.99) <0.0001
CKD vs no CKD	1.67 (1.49 – 1.86) <0.0001	1.88 (1.66 – 2.13) <0.0001	1.47 (1.31 – 1.64) <0.0001	
COPD vs no COPD	1.64 (1.50 – 1.81) <0.0001	1.78 (1.60 – 1.98) <0.0001	1.75 (1.60 – 1.91) <0.0001	1.58 (1.44 – 1.74) <0.0001
DM vs no DM	1.48 (1.37 – 1.60) <0.0001	1.51 (1.51 – 1.39) <0.0001	1.45 (1.35 – 1.56) <0.0001	1.38 (1.28 – 1.49) <0.0001
HLP vs no HLP	0.74 (0.70 – 0.80) <0.0001	0.77 (0.72 – 0.83) <0.0001		0.76 (0.71 – 0.82) <0.0001
HF vs no HF	1.65 (1.52 – 1.78) <0.0001	1.54 (1.40 – 1.69) <0.0001	1.65 (1.54 – 1.78) <0.0001	1.55 (1.43 – 1.68) <0.0001
HTN vs no HTN	0.96 (0.89 – 1.03) 0.3022	1.01 (0.93 – 1.09) 0.8735	0.95 (0.89 – 1.02) 0.0.1532	0.85 (0.79 – 0.91) <0.0001
Stroke vs no stroke	1.32 (1.12 – 1.57) 0.0004	1.20 (0.98 – 1.46) 0.0735	1.28 (1.09 – 1.51) 0.0060	1.45 (1.23 – 1.71) <0.0001
BMI	0.99 (0.98 – 0.99) 0.0130			
LVEF < 50% vs ≥ 50%		1.36 (1.26 – 1.48) <0.0001		
Sodium, ≤135 vs > 135 mmol/l				1.12 (1.03 – 1.22) 0.0055
BUN ≤ 19 vs ≥20 mg/dl				0.79 (0.73 – 0.85) <0.0001
Creatinine ≤1.5 vs >1.5 mg/dl				0.66 (0.55 – 0.66) <0.0001
LDL-C, Q2 vs Q1			0.90 (0.83 – 0.99) 0.0240	
LDL-C, Q3 vs Q1			0.87 (0.79 – 0.95) <0.0033	
LDL-C, Q4 vs Q1			0.83 (0.75 – 0.92) <0.0003	

Heart Failure

Variables	Model 1 HR (95% CI) P value	Model 2 HR (95% CI) P value	Model 3 HR (95% CI) P value	Model 4 HR (95% CI) P value
Age	1.03 (1.03 – 1.04) <0.0001	1.04 (1.04 – 1.05) <0.0001	1.03 (1.03 – 1.04) <0.0001	1.04 (1.03 – 1.04) <0.0001
Gender	1.10 (1.03 – 1.19) 0.0010	1.11 (1.01 – 1.21) 0.0264	1.07 (0.98 – 1.15) 0.1144	1.02 (0.93 – 1.11) <0.0001
Ethnicity	1.18 (1.04 – 1.35) 0.0119	1.05 (0.87 – 1.25) 0.6243	1.14 (1.00 – 1.31) <0.0462	1.13 (0.97 – 1.32) 0.1155
Length of stay	1.02 (1.01 – 1.02) <0.0001	1.02 (1.01 – 1.02) <0.0001	1.02 (1.01 – 1.02) <0.0001	1.04 (1.01 – 1.02) 0.0005
Cancer vs no cancer	1.43 (1.30 – 1.57) <0.0001	1.44 (1.28 – 1.62) <0.0001	1.34 (1.19 – 1.49) <0.0001	1.41 (1.25(1.59) <0.0001
CKD vs no CKD	1.50 (1.39 – 1.62) <0.0001	1.72 (1.56 – 1.89) <0.0001	1.48 (1.36 – 1.62) <0.0001	
COPD vs no COPD	1.16 (1.07 – 1.26) 0.0004	1.25 (1.13 – 1.39) <0.0001	1.19 (1.08 – 1.30) 0.0002	1.23 (1.11 – 1.36) <0.0001
DM vs no DM	1.14 (1.06 – 1.23) 0.0005	1.13 (1.03 – 1.23) 0.0068	1.08 (1.00 – 1.17) 0.0450	1.08 (0.99 – 1.18) 0.0769
HLP vs no HLP	0.81 (0.76 – 0.87) <0.0001	0.83 (0.76 – 0.90) <0.0001		0.78 (0.72 – 0.85) <0.0001
CAD vs no CAD	1.03 (0.96 – 1.10) 0.4144	1.04 (0.96 – 1.14) 0.3457	1.02 (0.94 – 1.11) 0.5854	1.05 (0.96 – 1.14) 0.2684
HTN vs no HTN	0.97 (0.90 – 1.05) 0.4229	0.99 (0.90 – 1.08) 0.8029	0.95 (0.87 – 1.03) 0.2073	0.83 (0.85 – 1.02) 0.1386

Stroke vs no stroke	1.05 (0.86 – 1.28) 0.6273	1.17 (0.94 – 1.46) 0.1605	1.06 (0.86 – 1.30) 0.5812	1.01 (0.80 – 1.28) 0.9253
BMI	0.99 (0.98 – 0.99) <0.0001			
LVEF < 50% vs ≥ 50%		1.07 (0.98 – 1.17) 0.1328		
Sodium, ≤135 vs > 135 mmol/l				1.35 (1.23 – 1.48) <0.0001
BUN ≤ 19 vs ≥20 mg/dl				0.83 (0.74 – 0.92) 0.0007
Creatinine <1.5 vs ≥1.5 mg/dl				0.76 (0.70 – 0.84) <0.0001
LDL-C, Q2 vs Q1			0.89 (0.81 – 0.98) 0.0197	
LDL-C, Q3 vs Q1			0.82 (0.74 – 0.92) <0.0003	
LDL-C, Q4 vs Q1			0.77 (0.68 – 0.87) <0.0001	

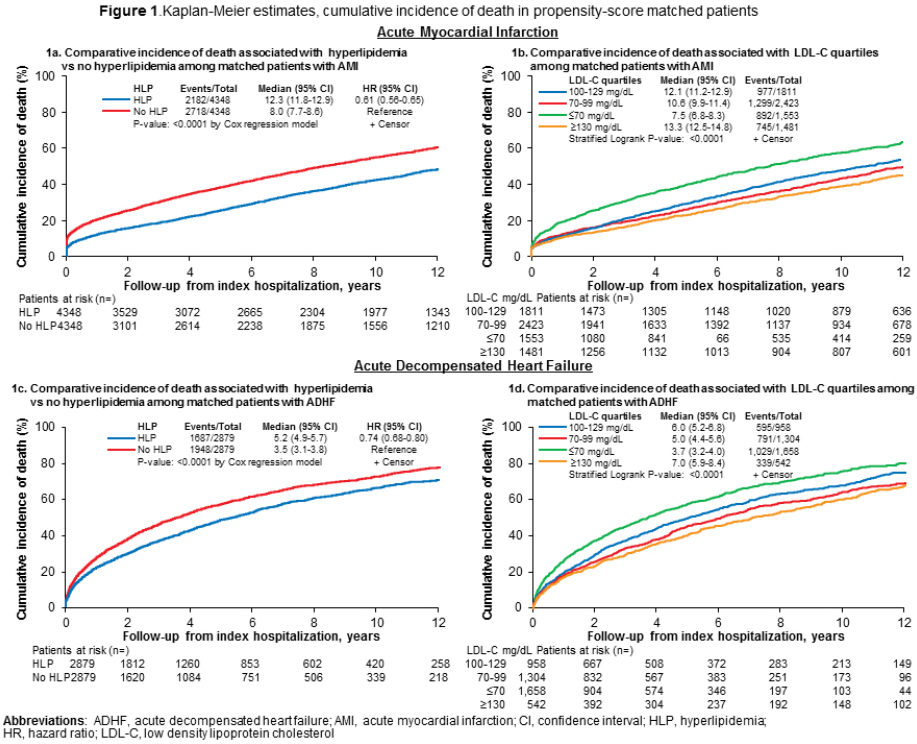


Figure 1. Kaplan-Meier estimates, cumulative incidence of death in propensity-score matched patients

81x60mm (300 x 300 DPI)

Figure 2. Forest plot, based on Cox regression analysis by robust variance estimator to account for matching, showing comparison of mortality estimates across specific single covariate and paired covariates, combined hyperlipidemia and one of the other comorbid condition.

Figure 2A: Propensity score-matched acute myocardial infarction cohort

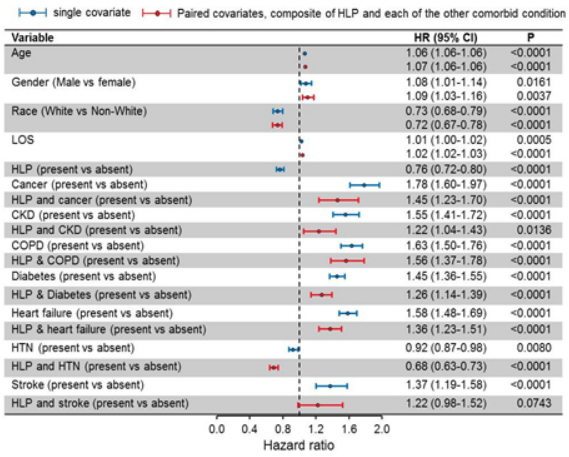
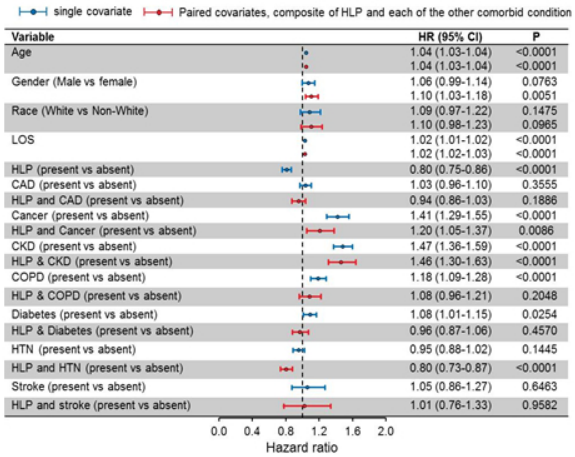


Figure 2B: Propensity score-matched heart failure cohort



Abbreviations: CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HLP, hyperlipidemia; HR, hazard ratio; HTN, hypertension; LOS length of stay

Figure 2. Forest plot, based on Cox regression analysis by robust variance estimator to account for matching, showing comparison of mortality estimates across single covariate and paired covariates, combined hyperlipidemia and one of the other comorbid condition.

60x81mm (300 x 300 DPI)

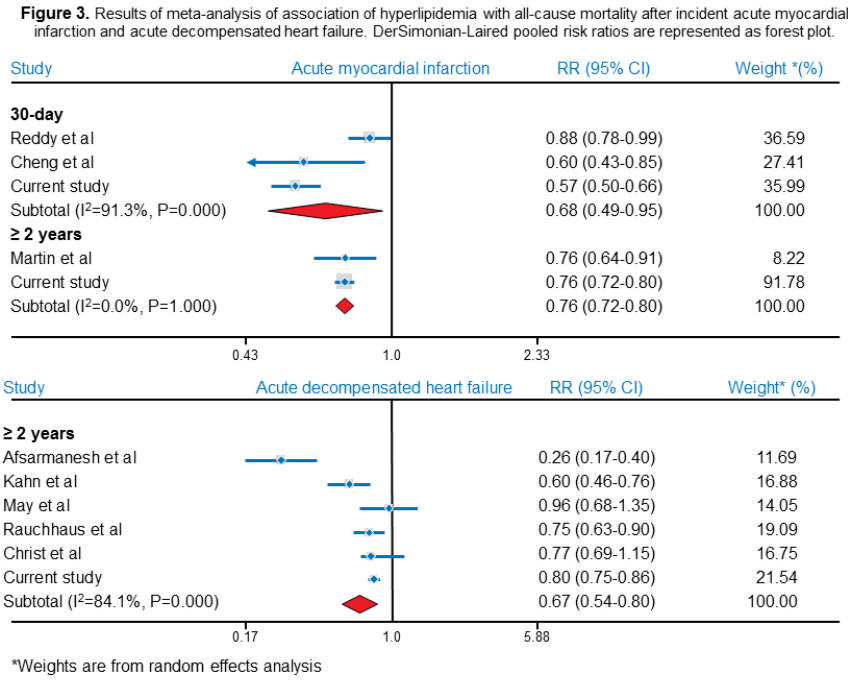


Figure 3. Results of meta-analysis of the association of hyperlipidemia with all-cause mortality after incident acute myocardial infarction and heart failure. DerSimonian-Laired pooled risk ratios are represented as forest plot.

81x60mm (300 x 300 DPI)

Supplementary Material

Title:

Hyperlipidemia is associated with lower mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity matched cohort study and a meta-analysis

Study coauthors:

Mohammed Yousufuddin, Paul Takahashi, Brittny Major, Eimad M. Ahmmad, Hossam M. Al-Zu'bi, Jessica Shultz, Taylor Doyle, Kelsey Jensen, Umesh Sharma, Zhen Wang, Vinaya Simha, Mohammad H. Murad,

1. **Search strategy**
2. **Supplement Table 1.** *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for two index conditions used in the study
3. **Supplement Table 2.** Characteristics of included studies and participants
4. **Supplement Table 3.** Assessment of risk of bias using Newcastle-Ottawa scale
5. **Supplement Figure 1.** STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram of the process of selection of study cohorts
6. **Supplement Figure 2.** PRISMA flow diagram of evidence search and selection of studies for meta-analysis
7. **Supplement Figure 3.** Supplemental figure 3. Love plot showing standardized differences for baseline covariates comparing original propensity-score unmatched to propensity-score matched samples, acute myocardial infarction cohort (left panel) and heart failure cohort (right panel)

SEARCH STRATGY

Ovid search strategy

Database(s): Embase 1988 to 2018 Week 08, EBM Reviews - Cochrane Central Register of Controlled Trials January 2018, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

#	Searches	Results
1	exp Myocardial Infarction/	464828
2	exp heart infarction/	293249
3	(("coronary arter*" adj3 occlusion) or (heart adj2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*").ti,ab,hw,kw.	606258
4	1 or 2 or 3	608529
5	acute.ti,ab,hw,kw. and 4	239685
6	exp Heart Failure/	498877
7	(((heart or cardiac or myocardial) adj2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis").ti,ab,hw,kw.	519250
8	6 or 7	633042
9	exp Pneumonia/	313860
10	("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*").ti,ab,hw,kw.	533949
11	9 or 10	549542
12	5 or 8 or 11	1350218
13	exp Hyperlipidemias/	192450
14	("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous	252850

	xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex").ti,ab,hw,kw.	
15	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu, dt	80348
16	(Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*).ti,ab,hw,kw.	208226
17	Dyslipidemias/	20270
18	(dyslipidemia or dyslipoproteinemia).ti,ab,hw,kw.	92147
19	or/13-18	481133
20	12 and 19	47704
21	exp survival/	902536
22	exp death/	717663
23	exp mortality/	1191292
24	mortality.fs.	506650
25	exp survival analysis/	274790
26	(surviv* or death* or mortalit* or fatalit*).ti,ab,hw,kw.	5314876
27	or/21-26	5623459
28	20 and 27	24286
29	(exp animals/ or exp nonhuman/) not exp humans/	8998409
30	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.	7727415
31	28 not (29 or 30)	23991

32	limit 31 to english language	22671
33	limit 32 to (conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,CCTR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	4951
34	32 not 33	17720
35	exp controlled study/	5856381
36	exp Randomized Controlled Trial/	924372
37	exp triple blind procedure/	179
38	exp Double-Blind Method/	405536
39	exp Single-Blind Method/	72408
40	exp latin square design/	348
41	exp Placebos/	330956
42	exp Placebo Effect/	10111
43	exp comparative study/	2771403
44	exp intervention studies/	34956
45	exp Cross-Sectional Studies/	500737
46	exp Cross-Over Studies/	128902
47	exp Cohort Studies/	2186646
48	exp longitudinal study/	344882
49	exp retrospective study/	1277886
50	exp prospective study/	963919
51	exp clinical trial/	2029131
52	clinical study/	106532
53	exp case-control studies/	1046859
54	exp confidence interval/	162834
55	exp multivariate analysis/	475730
56	((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (random* adj1 allocat*) or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or	18012184

	((study or trial or random* or control*) and compar*)).mp,pt.	
57	or/35-56	18453897
58	34 and 57	14467
59	exp *Hyperlipidemias/ or exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu, dt or *Dyslipidemias/ or ("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex" or (Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*) or (dyslipidemia or dyslipoproteinemia)).ti.	170773
60	exp *Myocardial Infarction/ or exp *heart infarction/ or exp *Heart Failure/ or exp *Pneumonia/ or (("coronary arter*" adj3 occlusion) or (heart adj2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*" or (((heart or cardiac or myocardial) adj2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis") or ("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*")).ti.	716170
61	58 and (59 or 60)	6960
62	limit 61 to yr="2013 -Current"	2705
63	remove duplicates from 62	2017
64	61 not 62	4255
65	remove duplicates from 64	3291
66	63 or 65	5308
67	5 and 66	2924
68	from 67 keep 1-1890	1890
69	from 68 keep 1-1000	1000

70 from 68 keep 1001-1890	890
71 from 67 keep 1950-2924	975
72 from 67 keep 1891-1949	59
73 66 not 67	2384
74 8 and 73	2199
75 from 74 keep 1-1654	1654
76 from 75 keep 1-1000	1000
77 from 75 keep 1001-1654	654
78 from 74 keep 1655-1710	56
79 from 74 keep 1711-2199	489
80 73 not 74	185
81 from 80 keep 1-100	100
82 from 80 keep 111-185	75
83 from 80 keep 101-110	10

Scopus search strategy

1	TITLE(("coronary arter*" W/3 occlusion) or (heart W/2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*") AND TITLE-ABS-KEY(acute)
2	TITLE(((heart or cardiac or myocardial) W/2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis")
3	TITLE("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*")
4	1 or 2 or 3
5	TITLE("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex")
6	TITLE(Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*)
7	TITLE(dyslipidemia or dyslipoproteinemia)
8	5 or 6 or 7
9	TITLE-ABS-KEY(surviv* or death* or mortalit* or fatalit*)
10	LANGUAGE(english)
11	TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (random* W/1 allocat*) or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or

	"case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*))
12	4 and 8 and 9 and 10 and 11
13	TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))
14	12 and not 13
15	DOCTYPE(ab) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
16	14 and not 15
17	PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
18	16 and not 17
19	TITLE(("coronary arter*" W/3 occlusion) or (heart W/2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*") AND TITLE-ABS-KEY(acute)
20	18 and 19
21	TITLE(((heart or cardiac or myocardial) W/2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis")
22	(18 and not 20) and 21
23	18 and not (20 or 22)

SUPPLEMENT TABLE 1

Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for index conditions used in the study.

Diagnosis	*ICD-9-CM* Codes
Acute myocardial infarction	410.00, 410.01, 410.10, 410.11, 410.20, 410.21, 410.30, 410.31, 410.40, 410.41, 410.50, 410.51, 410.60, 410.61, 410.70, 410.71, 410.80, 410.81, 410.90, 410.91
Heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40,

SUPPLEMENT TABLE 2. Characteristics of studies and participants included in meta-analysis

Condition	F/U	Study	Year	Design	N =	Mean age, year	Lipid type	End point	Covariates
AMI	30-day	Cheng et al[1]	2015	observational study	724	68	LDL-C, TG-C	Death	Age, HTN, DM, smoking, family history of CAD, alcohol consumption, ESRD
		Reddy et al[2]	2015	Observational /Registry	115492	67	LDL-C, HDL-C	Death	Age, sex, race, HTN, previous CAD, DM, smoking, blood pressure, heart rate , previous PCI, previous CABG
		Current study	2018	Retrospective cohort	8,696	68	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use
	≥ 2 years	Martin et al[3]	2015	Prospective Substudy	2465	58	RLP-C, IDL-C, VLDL3-C, VLDL-C	Death	Age, sex, race, education, insurance, history of CAD, Dyslipidemia, DM, blood pressure, CKD, HF, CAD, prior PCI, Prior CABG, Smoking, BMI, activity time, alcohol use
		Current study	2018	Retrospective cohort	8,696	68	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use
Heart Failure	≥ 2 years	Afsarmanesh et al[4]	2006	Observational cohort	614	48	TC, LDL-C, HDL-C, TG-C	Death	Sex, age, HF etiology, NYHA, DM, smoking, HTN, BMI, LVEF
		Christ et al[5]	2005	Prospective cohort	422	50	LDL-C	Death	Age, sex, race, education, insurance, history of CAD, dyslipidemia, DM, blood pressure, CKD, HF, CAD, prior PCI, Prior CABG, Smoking, BMI, activity time, alcohol use
		Kahn et al[6]	2013	Observational study	2428	69.8	TC, LDL-C, HDL-C, TG-C	Death	Age, sex, HTN, DM, dyslipidemia, smoking, CKD, Cirrhosis, Statin use, BB use, ACE use, hydralazine use, nitrates use, Digoxin use, lipid level, sodium, hemoglobin, Creatinine, BUN, ALT, AST, albumin
		May et al[7]	2006	Registry	1641	65.5	TC, LDL-C, HDL-C, TG-C	Death	Age, sex, HTN, DM, family history of CAD, smoker, previous CAD, previous CVA, statin use, renal function ,BMI, ejection fraction
		Rauchhaus et al[8]	2003	Prospective cohort	303	62	TC	Death	Age, BMI, sodium, potassium, ESR, TNF, BUN, LVEF, lipid level, NYHA class, Cachexia, medication use (loop diuretic, ACE inhibitor, calcium channel blocker, digoxin, amiodarone, BB, lipid lowering, aspirin)
		Current study	2018	Retrospective cohort	5,758	73	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AMI, acute myocardial infarction; AST, aspartate aminotransferase; BB, beta blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CABG, Coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, Chronic Obstructive Pulmonary Disease; CVA, cerebrovascular accident; DM, Diabetes mellitus; ESRD, end stage renal disease; F/U, follow up; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; HLP, hyperlipidemia; HTN, hypertension; IDL-C, Intermediate-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; N=, number of patients; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RLP-C , remnant-like particles-cholesterol; TC, total cholesterol; TG-C, triglyceride-cholesterol; TNF, tumor necrosis factor; VLDL-C, very-low-density lipoprotein-cholesterol.

References

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2. Reddy VS, Bui QT, Jacobs JR, et al. Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). *Am J Cardiol.* 2015;115(5):557-562.
3. Martin SS, Faridi KF, Joshi PH, et al. Remnant Lipoprotein Cholesterol and Mortality After Acute Myocardial Infarction: Further Evidence for a Hypercholesterolemia Paradox From the TRIUMPH Registry. *Clin Cardiol.* 2015;38(11):660-667.
4. Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J.* 2006;152(6):1077-1083.
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SUPPLEMENT TABLE 3. Risk of Bias Assessment (Newcastle-Ottawa Scale)

			Selection				Compatibility		Outcome			
Condition	Study	Year	S1	S2	S3	S4	C1	C2	O1	Q2	O3	Quality
Acute Myocardial Infarction	Cheng et al[1]	2015	*	*	*		*	*	*			6
	Martin et al[2]	2015	*	*	*		*	*	*	*		7
	Reddy et al[3]	2015	*	*	*		*	*	*	*		7
Heart failure	Afsarmanesh et al[4]	2006	*	*	*		*	*	*	*	*	8
	Christ et al[5]	2005		*	*		*		*	*		5
	Kahn et al[6]	2013	*	*	*		*	*	*	*	*	8
	May et al[7]	2006	*	*	*	*	*	*	*	*	*	9
	Rauchhaus et al[8]	2003	*	*	*		*	*	*	*		7

NOTE: S1 = Representativeness of the exposed cohort. S2 = Selection of the non-exposed cohort. S3 = Ascertainment of exposure. S4 = Demonstration that the outcome of interest was not present at the start of the study. C1 = Comparability of the cohort on the basis of design. C2 = Comparability of the cohort on the basis of analysis. O1 = Assessment of outcome. O2 = Was the follow-up long enough for outcomes to occur? O3 = Adequacy of the follow-up of cohorts.

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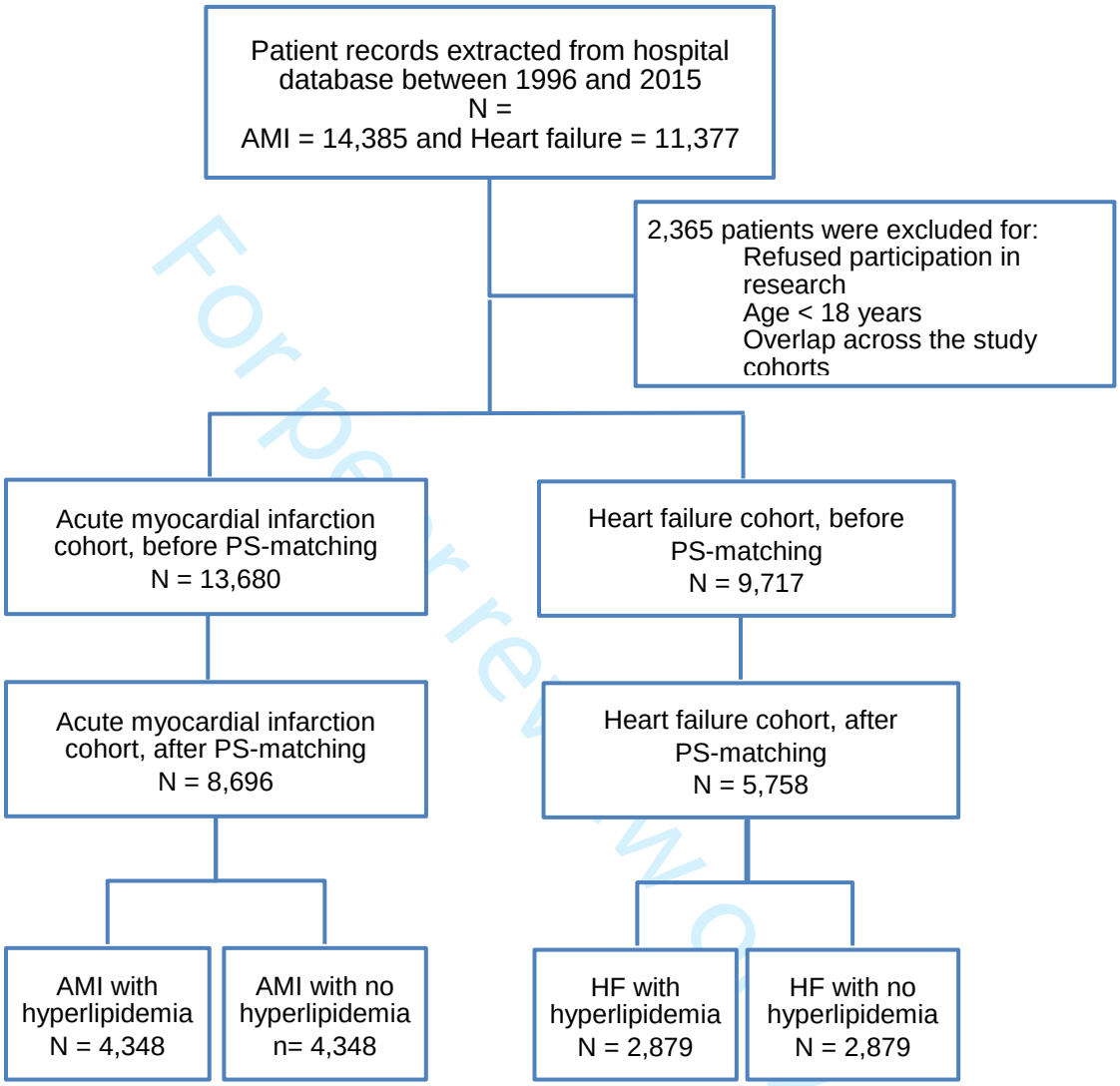
8. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42(11):1933-1940.

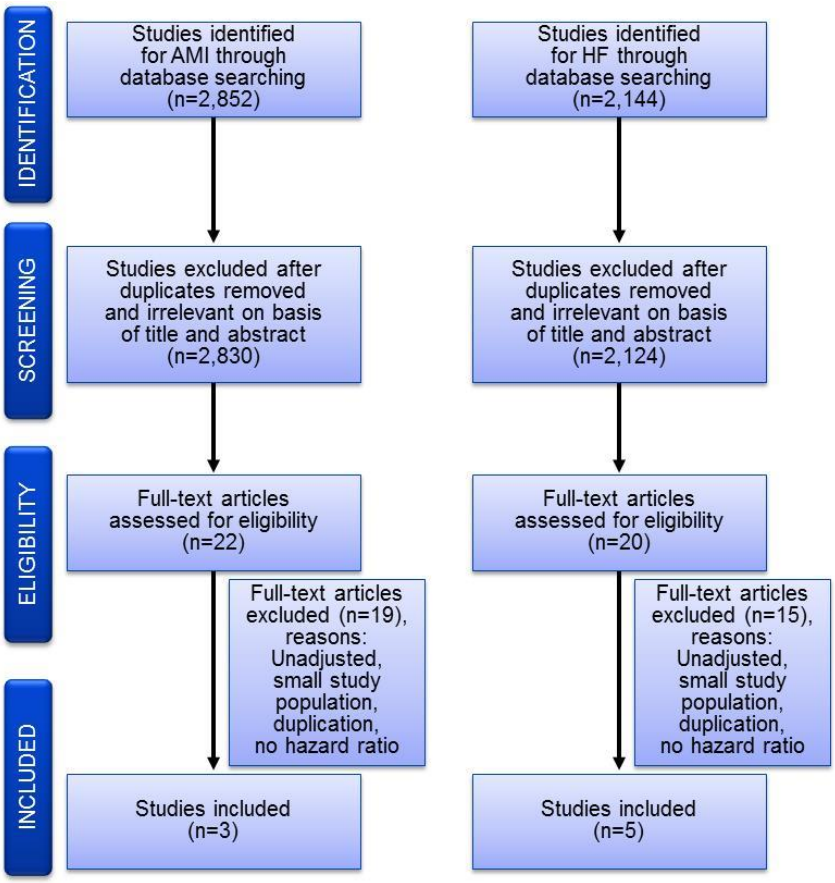
SUPPLEMENT FIGURE 1

Flow diagram. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram of the process of selection of study cohorts from Mayo Clinic Hospital Data Base



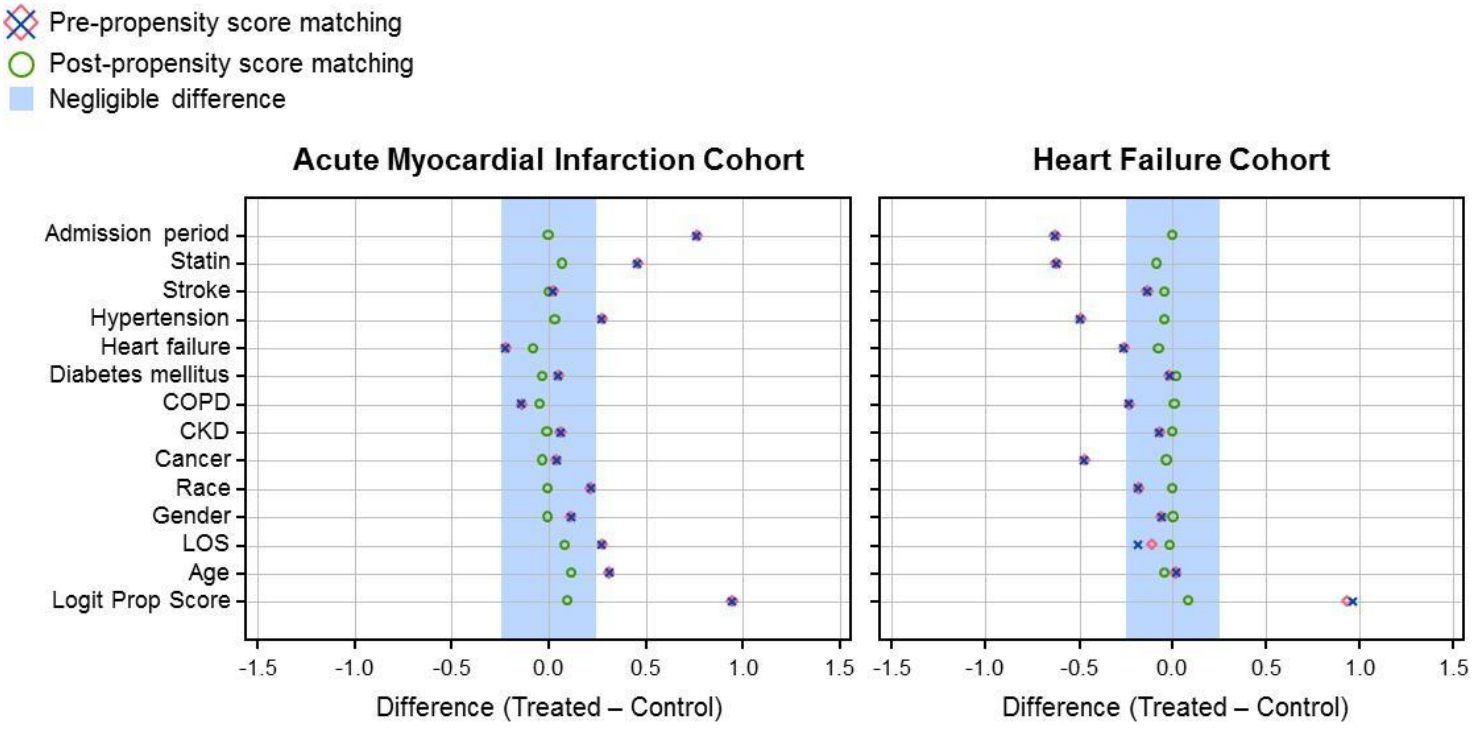
SUPPLEMENT FIGURE 2

PRISMA flow diagram of evidence search and selection of studies for meta-analysis



SUPPLEMENT FIGURE 3

Love plot showing standardized differences for baseline covariates comparing original propensity-score unmatched to propensity-score matched samples, acute myocardial infarction cohort (left panel) and heart failure cohort (right panel)



Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LOS, length of hospital stay

BMJ Open

Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

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Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

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Tables	3
Figures	3
References	63

ABSTRACT

Objective To examine the effect of hyperlipidemia (HLP), defined as having a preexisting or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥100 mg/dl during index hospitalization or within the preceding 6 months, on all-cause mortality after hospitalization for acute myocardial infarction (AMI) or acute decompensated heart failure (ADHF) and to determine whether HLP modifies mortality associations of other competing comorbidities. A systematic review and meta-analysis to place the current findings in the context of published literature.

Design Retrospective study, 1:1 propensity-score matching cohorts; a meta-analysis.

Setting Large academic center, 1996 to 2015

Participants Hospitalized patients with AMI or ADHF

Main outcomes and measures All-cause mortality and meta-analysis of relative risks (RR).

Results: Unmatched cohorts: 13,680 patients with AMI (age [mean] 68.5 ± [SD] 13.7 years; 7,894 [58%] with HLP) and 9,717 patients with ADHF (age, 73.1 ± 13.7 years; 3,668 [38%] with HLP). In matched cohorts, the mortality was lower in AMI patients (n = 4,348 pairs) with HLP vs no HLP, 5.9 vs 8.6/100 person-years of follow up, respectively (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.72 – 0.80). A similar mortality reduction occurred in matched ADHF patients (n = 2,879 pairs) with or without HLP (12.4 vs 16.3 deaths/100 person-years; HR 0.80, 95% CI 0.75 – 0.86). HRs showed modest reductions when HLP occurred concurrently with other comorbidities. Meta-analyses of 9 observational studies showed that HLP was associated with a lower mortality after incident AMI or ADHF (AMI: RR 0.72, 95% CI 0.69 – 0.76; HF: RR 0.67, 95% CI 0.55 – 0.81)

Conclusions: Among matched AMI and ADHF cohorts, concurrent HLP, compared with no HLP, was associated with a lower mortality and attenuation of mortality associations with other competing comorbidities. These findings were supported by a systematic review and meta-analysis.

Strengths and limitations of this study

- Cohort study comprised of patients with cardiologist-confirmed diagnoses, high rates of case ascertainments, and prompt mortality updates.
- Meta-analysis portion of the study adhered to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) Protocols.
- Large sample size and event rates and longer-term follow up allowed detailed assessment of the association of hyperlipidemia with mortality across multiple categories.
- 1:1 propensity scoring was used to match pairs of patients with concurrent hyperlipidemia and those with no hyperlipidemia for potential confounders.
- Limitations were inherent disadvantages of retrospective cohort studies, potential unmeasured confounders, *International Classification of Diseases, Ninth Revision, Clinical Modification* to identify study cohorts, ascertainment of comorbid conditions during index hospitalization, and lack of data on subsequent acquisition of these conditions during the follow-up.

Introduction

Early epidemiological studies of 1970s and 1980s including Framingham Heart Study[1], Multiple Risk Factor Intervention Trial (MRFIT)[2], Coronary Primary Prevention Study[3], and Helsinki Heart Study[4], all provided substantial evidence for the epidemiological relationship between cholesterol levels and incident coronary artery disease in general population. In 2007, a meta-analysis of individual data from 61 prospective studies suggested that total cholesterol was positively associated with cardiovascular mortality[5]. However, contemporary studies largely examined the effect of statins and other cholesterol

lowering interventions on cardiovascular events [6 7]. A similar relationship between hyperlipidemia (HLP) and incident heart failure (HF) has been reported [6-9]. Surprisingly, several recent studies found an inverse association wherein HLP, counterintuitively, conferred an overall survival benefit in patients with established acute myocardial infarction (AMI)[10-13] and HF[14]. Although cholesterol levels in general population predict new cardiovascular events, it is unclear whether a positive association persists after incident AMI or HF. Furthermore, the effect of HLP on the association of other competing conditions with mortality is unknown.

Systematic reviews and meta-analyses on the association of HLP with new AMI have already been published[5], but the clinical trials evaluating this relationship after the incident AMI have not been systematically reviewed. Additionally, the data are limited on the association between HLP and incident HF and subsequent mortality. A comprehensive review of published data on the association of HLP with mortality after incident AMI or HF would clarify these issues.

We postulated that if a diagnosis of HLP decreases the mortality after AMI or HF, then, it also lessens the magnitude of mortality risks associated with other competing comorbidities. We tested this hypothesis, separately, in large cohorts of patients hospitalized for incident AMI and acute decompensated HF (ADHF). To compare patients with and with no HLP, we assembled 1:1 balanced groups using propensity score-matching for each study condition. Our objectives were three-fold: 1) to estimate the association of HLP with all-cause mortality among patients with AMI or ADHF, 2) to determine the extent to which the association between other competing comorbidities[15] and mortality is modified by HLP 3) and to provide risk estimates for mortality associated with HLP after incident AMI or HF through systematic review and meta-analyses of published and current study data to place the current findings in the context of published literature.

Methods

Cohort study

STUDY POPULATION AND DATA COLLECTION

The study cohorts were comprised of adults aged ≥18 years, hospitalized at Mayo Clinic from August 1, 1996 to September 17, 2015 with primary discharge diagnoses of AMI or acute decompensated HF (ADHF) with follow up completed through August 17, 2016. AMI included both ST-elevation myocardial infarction (STEMI) and non-STEMI. ADHF comprised of heart failure with both reduced and preserved ejection fractions. Discharge diagnoses were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (presented in supplement table 1). Mayo clinic has one of the oldest and most advanced medical record systems in the United States. Patient provided information is constantly updated at every clinic or hospital visit at its main Rochester campus and at a network of clinics and hospitals across more than 60 communities in states of Iowa, Wisconsin, and Minnesota. Strengthening The Reporting of Observational studies in Epidemiology (STROBE) flow diagram of study cohorts' selection of is presented in supplement figure 1. Further details of data extraction are published elsewhere[16]. The study was approved by the Mayo Clinic Institutional Review Board and need for patient consent was waived.

ASCERTAINMENT OF ACUTE MYOCARDIAL INFARCTION AND ACUTE DECOMPENSATED HEART FAILURE

For each patient the primary discharge diagnosis, AMI or ADHF, was documented by the attending physician at the time of discharge, assigned ICD-9-CM code, and subsequently captured by the abstractors.

ASCERTAINMENT OF COMORBID CONDITIONS

We focused on a panel of 20 comorbid conditions (CCs) defined by Department of Health and Human Services [15] and identified by Clinical Classifications Software codes of US Healthcare Cost Utilization Project. CCs with prevalence < 3% were excluded from analysis. To ascertain the comorbid effect of HLP

on other concurrent condition, we paired HLP with other competing comorbidities within an individual patient.

ASCERTAINMENT OF HYPERLIPIDEMIA AND STATIN USE

HLP was defined as having a preexisting or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥100 mg/dl as clinically measured during index hospitalization or within the preceding 6-months. LDL-C was measured indirectly by Friedewald method[17]. Published reports suggest that lipid panel measured during the first 24 hours after an acute cardiovascular event reliably represents baseline level[18]. Statin use was based on discharge medication reconciliation.

ASCERTAINMENT OF MORTALITY

All deaths occurring from admission to censoring date of August 17, 2016 were abstracted from medical records. The mortality data is updated regardless of the cause of death, including death due to murders, suicides, or accidents. At the time of drafting the manuscript, Minnesota all-cause (including suicide, murder, misadventures, and natural) Electronic Death Certificate Data is current to December 31, 2018,

PATIENT FOLLOW-UP

All patients were followed from index hospitalization until death or censoring date of August 17, 2016 whichever occurred first.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in this study

Systematic review and meta-analysis

DATA SOURCE AND SEARCHES

This systematic review and meta-analysis was conducted in accordance with the established methods[19] and followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[20]. We searched of MEDLINE, EMBASE, Cochrane Library, Web of Science databases for eligible trials from inception through September 2017 with continued surveillance through February 2018 for trials

examining the associations of HLP with mortality. We identified clinical studies with the same PICO (population, condition/disease, intervention, control and at least one outcome) and objectives. Studies with incomplete data were excluded. Methodological details of the meta-analysis are published elsewhere[21]. The search strategy is presented in the supplement.

STUDY SELECTION

Eligibility criteria included: 1) randomized or non-randomized clinical trials of adults with AMI or HF, 2) comparator groups HLP or hypercholesterolemia vs HLP or hypercholesterolemia as defined by individual study investigators, and 3) mortality as the primary outcome or one of the outcomes.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

From the results of initial search, two investigators (EA and HA), working independently reviewed articles for eligibility on the basis of titles and abstracts. Studies that satisfied the inclusion and exclusion criteria were retrieved for full text review. Disagreements were resolved by consensus and retained conflicts were adjudicated by a third investigator (MY). We extracted the following data from each study: type of study, number of participants, age, gender, presence and absence of hyperlipidemia, length of follow-up, and outcome measures. Measure of association with clinical outcomes (hazard ratio [HR], odds ratio [OR], or relative risk [RR]) were abstracted. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies[22].

Statistical analysis

ALL Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA)

1. THE COHORT STUDY

Propensity score analysis[23]: We assembled 1:1 propensity score-matched pairs of patients with AMI or ADHF to balance the differences in baseline variables between patients with and without concurrent HLP. Propensity scores were estimated using logistic regression (PROC PS MATCH in SAS) based on age,

gender, length of stay, race, comorbidities, statin prescription on discharge, and time period (1996-2005 vs. 2006-2016). Standardized differences in the matched cohort ranged from 0.122 to 0.004. One-to-one nearest neighbor caliper matching was used to match patients based on the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score. We performed C-statistic as a measure of the ability of the propensity score to control confounders[24]. C-statistic for the model was 0.752 for acute myocardial infarction patients and 0.755 for heart failure patients. Patients were of exact match on gender, race and enrollment period. Patients without HLP were matched to one with HLP generating a quasi-randomized design whereby study groups (HLP vs no HLP) have had similar propensity for allocation to either group.

Kaplan-Meier estimates: Kaplan-Meier estimates were performed using propensity-score matched cohorts and stratified log-rank tests were used to compare survival curves.

Multivariable Cox models: Cox proportional hazards models were performed on the matched samples using a robust variance estimator to account for matching. Multiple models were constructed for estimating hazard ratios (HR) for mortality. Model 1 estimated HR and 95% confidence intervals (CI) for mortality associated with HLP and other CCs. Model 2 was extended to fit Model 1 plus statin therapy. Model 3 examined the comorbid effect of HLP in combination with other competing comorbidities.

Sensitivity analysis: We performed several sensitivity analyses to ascertain the degree of bias that might explain significant associations between HLP and mortality and to confirm the robustness of our findings. From propensity-score matched AMI and HF patients, we identified patients with available data related to BMI, LDL-C, left ventricular ejection fraction (LVEF), and serum concentrations of sodium blood urea nitrogen (BUN), and creatinine. We conducted sensitivity analyses using separate Cox proportional regression models by excluding 1) patients with no LDL-C data, 2) patients with no available data on levels of sodium, blood urea nitrogen (BUN), and creatinine, 3) patients with no

available data on body mass index (BMI), and 4) patients with no available data on left ventricular ejection fraction (LVEF).

2. THE META-ANALYSIS

The DerSimonian and Laird random-effects model was used to pool estimates across studies [25]. The results were expressed as relative risk (RR) and 95% CI. Heterogeneity was assessed using I^2 to reflect proportion of heterogeneity not attributable to chance[26]. The number of studies was insufficient to statistically evaluate publication bias. Characteristics of included studies (Supplement table 2), assessment of risk of bias (supplement table 3), and PRISMA flow diagram (Supplement figure 2) are presented in supplement. PRISMA check list is presented in supplement table 4. We pooled the effect sizes (in this case, hazard ratio) reported by the studies. We didn't pool the intercept of the models as most were not reported. Additionally, the methods to generate the pooled intercept are not well developed either.

Results

1. THE COHORT STUDY

Cohort study population

The supplemental Figure 1 illustrates the Strengthening the Reporting of Observational Studies in Epidemiology flow diagram for selection of final study cohorts: AMI (Initial cohort n = 13,680; propensity score-matched cohort n = 8,696 , pairs 4,348) and ADHF (Initial cohort n = 9,717; propensity score-matched cohort n = 5,758, pairs 2,879). STROBE checklist is presented in supplement table 5.

Baseline characteristics

Baseline characteristics for each study cohort, before and after propensity score-matching by HLP, are presented in Table 1. Baseline characteristics for matched patients in each cohort were balanced. Before matching, patients with HLP were younger, more likely to be males, and had lower rates of COPD and HF and high prevalence of chronic kidney disease (CKD) and hypertension in the AMI cohort. As these variables were balanced in propensity score-matching, a balanced cohort with standardized differences of <10% for baseline characteristics was created for final analysis. Supplement figure 3 illustrates a love plot of standardized differences before and after propensity-score matching to allow visualization of improvement in prognostic balance. Of 20 CCs, only 8 were included in final analysis for frequency ≥3%. Supplement table 4 and 5 represent PRISMA

MORTALITY

Acute myocardial infarction: In matched patients, mortality was significantly lower among patients with HLP vs those with no HLP (overall mortality 2,182 [50.2%] vs 2,718 [62.5%] or 5.9 vs 8.6 deaths/100 person-years of follow up, P <0.0001). Median and person-years of follow up was greater in matched patients with HLP (median 8.8 years, interquartile [IQ] 3.2 – 13.1 years, 37,068 person-years of follow-up) vs those with no HLP (median 6.3 years, IQ 1.4– 12.4 years, 31,569 person-years of follow-up).

Acute decompensated heart failure: In matched patients, mortality was significantly lower among patients with HLP vs those with no HLP (overall mortality 1,687 [58.6%] vs 1,948 [67.7%] or 12.4 vs 16.3 deaths/100 person-years of follow-up, p <0.0001). Median and person-years of follow up was greater in matched patients with HLP (Follow up: median 3.2 years, IQ 1.0 – 6.9 years, 13,577 person-years of follow-up) vs those with no HLP (median 2.5 years, IQ 0.7 – 6.2 years, 11,951 person-years of follow-up).

KAPLAN-MEIER ESTIMATES

Figure 1 displays Kaplan-Meier estimates of all-cause mortality by HLP in propensity-score matched samples of AMI or ADHF patients. Kaplan-Meier survival curves diverged immediately after hospitalization and then remained parallel during the follow-up in both AMI and ADHF cohorts. Log-rank *P*-value for patients with and with no HLP remained < 0.0001 for each index condition. In multiple sub-analyses, risk differences in mortality between patients with and without HLP persisted in age <65 and ≥65 years, male and female, white and non-White with log-rank p <0.0001 for all sub-groups.

COX PROPORTIONAL REGRESSION MODEL 1

The results are presented in Figure 2. HLP as compared with no HLP, was associated with a lower risk of death from any cause after AMI (HR 0.76, 95% confidence interval [CI] 0.72 – 0.80, n = 8,696) or ADHF (HR 0.80, 95% CI 0.75 – 0.86, n = 5,758). Findings did not change significantly with exclusion of patients with a new in-hospital HLP diagnosis in sensitivity analysis. Co-occurrence of cancer, CKD, COPD, diabetes mellitus, HF, or stroke independently increased mortality following AMI or ADHF. While hypertension reduced mortality by 8% (95% CI 0.87 – 0.98) after AMI, neither hypertension nor CAD influenced mortality after ADHF hospitalization.

COX PROPORTIONAL REGRESSION MODEL 2

In separate analysis, adjustment of Cox proportional model for statin treatment did not change results for baseline HLP in predicting the all-cause mortality (AMI: HR 0.69, 95% CI 0.65 - 0.73; ADHF: HR 0.78, 95% CI 0.73-0.83).

COX PROPORTIONAL REGRESSION MODEL 3

The results of Cox model 3 are shown in Figure 2. Magnitude of HRs for mortality associated with cancer, COPD, CKD, diabetes, heart failure, and stroke were all modestly attenuated with concurrent HLP across

study cohorts. By comparison, protective effect of HLP on mortality was enhanced when paired with HTN in both AMI (HR 0.77, 95% CI 0.72- 0.83) and ADHF (HR 0.86, 95% CI 0.78-0.94).

SENSITIVITY ANALYSIS WITH AVAILABLE DATA ON FOLLOWING COVARIATES

1. *BMI*: Of 8,646 patients with AMI 6,092, and of 5,758 patients with HF, 5,311 have data for BMI. The association of HLP with mortality remained unchanged when multivariable model accounted for BMI. BMI was inversely related to mortality with 1 unit increase in BMI resulting in 1% reduction in mortality in both AMI (HR 0.99, 95% CI 0.98 – 0.99, P = 0.0130) and HF (HR 0.99, 95% CI 0.98 – 0.99, P <0.0001) cohorts (table 2)
2. *LDL-C on or within 6-months preceding admission:* Overall, 7,268 patients (84%) in AMI cohort and 4,562 patients (79%) in HF cohort had LDL-C clinically measured on or within 6-month preceding hospitalization. We stratified patients into quartiles according to levels of LDL-C, <70 mg/dl, 70 – 99 mg/dl, 100 – 129 mg/dl, and ≥ 130 mg/dl. There was a graded reduction in mortality from highest to the lowest LDL-C quartile in both AMI and HF (table 2).
3. *Levels of sodium, BUN, and creatinine.* AMI: 7,603 (87%), 6609 (70%), and 7,812 (90%) had data available on sodium, BUN, and creatinine respectively. HLP remained an independent predictor of lower mortality compared to no HLP when accounted for levels of sodium (≤ 135 vs >135 mmol/l), BUN (≤ 19 vs >19), and creatinine (≤ 1.5 vs >1.5) (Table 2). HF: 7,603 (87%), 6609 (70%), and 7,812 (90%) had data available on sodium, BUN, and creatinine respectively. HLP remains an independent predictor of lower mortality compared to no HLP when accounted for levels of sodium (≤ 135 vs >135 mmol/l), BUN (≤ 19 vs >19), and creatinine (≤ 1.5 vs >1.5) (Table 2).
4. *LVEF:* A total of 5,408 patients (62%) with AMI and 3,869 patients (67%) patients with ADHF had data available on LVEF, measured clinically during or within 6 months preceding hospitalization. HLP remained an independent predictor of lower mortality compared to no HLP when adjusted for LVEF in AMI and ADHF (Table 2).

2. META-ANALYSIS

Hyperlipidemia was associated with lower all-cause mortality after AMI (≤30-day mortality: 4 studies[10 27 28], n = 124,912, RR 0.66, 95% CI 0.45 – 0.97; long-term mortality [≥ 2 years]: 2 studies[29], n = 11,161, RR 0.72, 95% CI 0.69-0.76) and ADHF (long-term mortality [≥ 2 years]: 6 studies[30-34], n = 11,166, RR 0.67, 95% CI 0.55 – 0.81). Meta-analysis of AMI was homogenous (I^2 0%), however, substantial heterogeneity was noted in heart failure meta-analysis reflecting different settings in the observational studies. The results of meta-analysis are presented as forest plots (Figure 3).

Discussion

MAIN FINDINGS

This propensity-score matched study of large cohorts of patients hospitalized for AMI or ADHF and a systematic review with meta-analysis provided a rigorous assessment of the association between HLP and long-term all-cause mortality. First, a diagnosis of HLP, compared to no HLP, was associated with 24% and 20% relative risk reduction in all-cause mortality corresponding to 27 and 39 fewer deaths per 1000 person-years after incident AMI and ADHF, respectively. The reduced mortality associated with HLP was robust to adjustment for potential confounder including demographics, clinical characteristics, and key CCs. The association was consistent across the following subsets: young and old, male and female, white and non-white, and prevailed across both study cohorts. The reductions in mortality were independent of benefit attributable to statin therapy. Kaplan-Meier estimates suggest that the reduction in cumulative incidence of death from HLP begins immediately after hospitalization and is maintained into follow-up both in AMI and HF cohorts. Second, we found that cancer, COPD, CKD, diabetes mellitus, heart failure, or stroke, were all significantly associated with increased long-term mortality. This increased risk was offset by the lower mortality from HLP resulting in attenuation or even a null effect on mortality in patients with AMI or ADHF who had HLP concurrent with other CCs.

By comparison, hypertension, while having no effect in HF, was inversely associated with mortality in AMI similar to HLP. The magnitude of mortality reduction associated HLP was enhanced in the presence of HTN after incident AMI and ADHF. Third, the complementary meta-analysis of published observational studies and current study data demonstrated consistent results and provide further evidence that HLP is associated with decreased mortality following incident AMI or ADHF. Multiple sensitivity analyses among patients with available data on BMI, LDL-C, LVEF, levels of sodium, BUN, and creatinine were all yielded similar results and the association between HLP and mortality remained robust in AMI and ADHF.

COMPARITVE STUDIES

The association of hyperlipidemia with atherosclerotic cardiovascular disease is largely based on epidemiological studies [1-4] and randomized clinical trials of LDL-C lowering therapy. These studies have important limitations and do not ascertain causal relationship. Although genetic studies are promising and have the potential to address causal relationship of LDL-C with atherosclerotic cardiovascular disease[35], the co-inheritance of other pro-atherogenic factors that affect atherosclerotic cardiovascular disease may not be determined[36]. Findings of this study dispute general assumption that hyperlipidemia is associated with increased mortality. However, several community- and hospital-based population studies contradict this notion and support our findings. A number of large community-based population studies from Scandinavian countries showed that hyperlipidemia is inversely related to mortality, particularly in older adults [37-40]. These observations were reproduced in large community-based prospective cohort studies from Japan[41]. A prospective observational study found that low LDL-C on admission was associated with a lower 3-year survival after hospitalization for non-ST elevation myocardial infarction[42]. An earlier systematic review found that the mortality risk from HLP decreased with increasing age[5]. By comparison, we found that HLP maintained its survival benefit even in older adults, a finding supported by a meta-analysis of 19 cohort studies that showed inverse association

between elevated cholesterol and mortality[43]. These observations were reinforced by widely used risk-prediction models for AMI and HF in which HLP did not make into the final prediction models [12 13 44-46] suggesting a weaker or no association with mortality. An inverse relationship between HLP and mortality was reported for a number of other conditions not the focus of this study[47-49]. Similarly, numerous other conditions such hypertension, cigarette smoking, and factor V Leiden exhibit epidemiological paradox[50-52]. According to epidemiologists, these paradoxes may exemplify collider or index event bias wherein established risk factor for first occurrence of a disease becomes inversely related after the occurrence of an event [53-55]. The effect of HLP might be concealed in the presence of stronger competing risk factors for mortality [56]. Other potential mechanisms include a progressive increase in proportion of deaths from non-cardiovascular conditions with differential association with baseline cholesterol [57] and a reverse causation, whereby underlying disease lowers the cholesterol level and increases the risk of death. Numerous investigators argued that low cholesterol represents a biological marker for concurrent cachexia, malnutrition, cancer, and other chronic diseases with proven adverse impact on survival [58 59]. However, HLP remained a predictor of lower mortality in several studies that even excluded terminal diseases [43]. Our results support the concept of obesity paradox among patients with HF and AMI and findings were consistent with several published studies. Previous studies reported that even healthy subjects with low cholesterol are especially predisposed to infectious diseases [60-62]. Although our findings were adjusted for cancer and numerous other CCs, the potential confounding by undiagnosed cachexia or malnutrition cannot be excluded. Our findings were contradicted by a number of randomized clinical trials and meta-analyses of statin therapy in AMI that demonstrated a dose dependent decrease in the risk of cardiovascular events with reduction in LDL-C level, even down to <70 mg/dl[6]. These discrepant findings are attributable to demographic differences, patient population with lower rates of CCs, shorter follow-up intervals, and focus on cardiovascular events including cardiovascular mortality rather than all-cause mortality as the outcome.

CLINCAL IMPLICATIONS

The findings of this study, if validated, should reinforce the importance of HLP in predicting long-term mortality after index AMI or ADHF and potentially provide guidance for subsequent management. HLP can readily be diagnosed and help recognize AMI and HF patients with lower long-term mortality. In these patients, clinical care should not focus on certain lipid targets; rather evidence-based secondary prevention strategies should be initiated. Conversely, patients with AMI and ADHF without HLP may be considered to have increased risk for early mortality and potentially alert providers for close monitoring during hospitalization and after discharge. Both categories of patients would profit from thoughtful tailored programs with distinctive goals of care for existing CCs.

STRENGTHS AND LIMITATIONS

This study has several strengths. Firstly, large study cohorts, high level of case ascertainment for incident events and prompt mortality update[63] allowed precise estimation of mortality risks. Broader range of patient population, long follow-up extending to 20 years, and all-cause rather than cardiovascular mortality as the primary outcome are additional advantages over randomized controlled trials. Secondly, propensity-score matching to balance observed patient-characteristics enabled further control of potential differences. Thirdly, we conducted a systematic review and meta-analysis to place the findings of this study in the larger context of existing literature with consistent findings. The study also has a number of important limitations. These included possibility of unmeasured confounders, reliance on ICD-9-CM codes to identify study cohort, Clinical Classifications Software codes to assess coexisting CCs, ascertainment of CCs during index hospitalization, and lack of data on subsequent acquisition of these conditions during the follow up. Our study cohorts were homogenous with respect to race and substantially older than those observed in most clinical trials, but, similar to those in many epidemiological studies. The pre-existing hyperlipidemia and CCs were physician-diagnosed during

index hospitalization rather than being assigned by study investigators. Meta-analysis of ADHF was associated with heterogeneity; nevertheless, the results from all the included studies suggested a reduction in mortality with HLP. Despite some limitations, the findings of the present study may be extended to hospital-based, AMI and ADHF population at large.

CONCLUSIONS

The current findings, based on large unselected hospital-based patient-populations, provide strong evidence that after incident AMI or ADHF, a diagnosis of HLP, compared to no HLP, was associated with reduced long-term mortality, a longer median survival, and modest attenuation of the magnitude of mortality risk associated with other competing CCs. Our data support a protective role for HLP against all-cause mortality following incident AMI and ADHF. Further studies are needed to understand the complex relationship between HLP and mortality, especially in the presence of other competing comorbidities and to define appropriate HLP targets to maximize the benefits.

Footnotes

Contributors MY, PYT, KJ, EA, JP, TD, ZW, VS, and MHM contributed to the initial conception of the study. MY, PYT, BM, EA, HA, JP, TD, KJ, RYA, US, AS, ZW, VS, and MHM made substantial contributions to the statistical methodology, analysis and data interpretation. MY, EA, JP, TD, KJ wrote the first draft of the manuscript. MY, PT, BM, EA, HA, JP, TD, KJ, RYA, US, AS, ZW, VS, and MHM provided substantial revisions to the manuscript. All authors approved the final version of the protocol.

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Table 1. Patient characteristics and standardized differences before and after propensity score-matching

Acute myocardial infarction							
		All Patients (n=13,680)			Propensity score-matched cohort (n=8,696)		
Variables		With hyperlipidemia n=8,929	With no hyperlipidemia n=4,751	Absolute Standardized Difference	With hyperlipidemia n=4,348	With no hyperlipidemia n=4,348	Absolute Standardized Difference
Demographics	Age, y, mean ± SD	67.0 ± 13.6	71.3 ± 13.5	0.315	68.9 ± 13.3	70.6 ± 13.6	0.122
	Male n = (%)	6,035 (68)	2,938 (62)	0.121	2,761 (64)	2,761 (64)	0
	White n= (%)	8,108 (91)	3,963 (83)	0.222	3,744 (86)	3,744 (86)	0
Anthropometric measurements	BMI kg/m^2	30.1 ± 6.2	28.8 ± 6.3	-	29.8 ± 6.3	28.9 ± 6.3	-
	BMI, missing n = (%)	1,556 (17)	1,520 (32)	-	1,274 (29)	1,330 (31)	-
Clinical characteristics	LOS, days, median (quartiles 25%-75%)	3 (2-5)	4 (3-8)	0.275	4 (3-6)	4 (3-7)	0.086
Year of hospital admission	1996-2005 n = (%) 2006-2016 n = (%)	3886 (44) 5043 (57)	3732 (79) 1019 (21)	0.770	3341 (77) 1007 (23)	3341 (77) 1007 (23)	0
Comorbid conditions	CAD, n = (%)	-	-		-	-	
	Cancer, n = (%)	744 (8)	342 (7)	0.042	279 (6)	313 (7)	0.029
	CKD, n = (%)	885 (12)	380 (8)	0.067	348 (18)	353 (8)	0.004
	COPD, n = (%)	820 (9)	640 (14)	0.136	482 (11)	543 (13)	0.044
	Diabetes, n = (%)	2,567 (29)	1,249 (26)	0.055	1,091 (295)	1,149 (26)	0.030
	Heart failure, n = (%)	1,762 (20)	1,376 (29)	0.216	1,033 (24)	1,173 (27)	0.075
	Hypertension, n = (%)	6,049 (68)	2,584 (54)	0.277	2,530 (58)	2,453 (56)	0.037
	Stroke, n = (%)	359 (4)	168 (4)	0.025	151 (4)	148 (3)	0.004
Lipid levels	LDL-C mg/dl	110.9 ± 39.2	78.7 ± 25.0	-	118.4 ± 37.6	78.8 ± 25.1	-
	LDL-C, missing n = (%)	483 (5)	1,356 (29)	-	251 (6)	1,177 (27)	-
Drug treatment	Statin	4,665 (52)	1,431 (30)	0.461	1,566 (36)	1,412 (33)	0.074

Heart Failure

Variables		All Patients (n=9,717) With hyperlipidemia n=3,941	All Patients (n=9,717) With no hyperlipidemia n=5,776	All Patients (n=9,717) Absolute Standardized Difference	Propensity score-matched cohort (n=5,758) With hyperlipidemia n=2,879	Propensity score-matched cohort (n=5,758) With no hyperlipidemia n=2,879	Propensity score-matched cohort (n=5,758) Absolute Standardized Difference
Demographics	Age, y, mean ± SD	73.2 ± 12.4	73.0 ± 14.5	0.020	72.6 ± 12.6	73.1 ± 14.1	0.040
	Male n = (%)	2,342 (59)	3,266 (57)	0.058	1,682 (54)	1,682 (54)	0
	White n = (%)	3,574 (91)	4,896 (85)	0.181	2,588 (90)	2,588 (90)	0
Anthropometric measurements	BMI kg/m^2	31.1 ± 7.6	29.7 ± 7.5	-	31.0 ± 7.6	30.0 ± 7.5	-
	BMI, missing n = (%)	193 (5)	780 (13)	-	185 (6)	262 (9)	-
Clinical characteristics	LOS, days, median (quartiles 25%-75%)	4 (2 – 6)	4 (2 – 7)	0.183	4 (2 – 6)	4 (2 – 7)	0.018
Year of hospital admission	1996-2005 n = (%) 2006-2016 n = (%)	1221 (31) 2720 (69)	3510 (61) 2266 (39)	0.626	1197 (42) 1682 (58)	1197 (42) 1682 (58)	0
Comorbid conditions	CAD, n = (%)	2,482 (63)	2,309 (40)	0.472	1,580 (55)	1,537 (53)	0.031
	Cancer, n = (%)	595 (15)	736 (13)	0.068	419 (15)	420 (15)	0.001
	CKD, n = (%)	1,286 (33)	1,299 (23)	0.228	802 (28)	819 (28)	0.013
	COPD, n = (%)	813 (21)	1,152 (20)	0.017	567 (20)	584 (20)	0.015
	Diabetes, n = (%)	1,617 (41)	1,660 (29)	0.260	1,117 (39)	1,015 (35)	0.075
	Heart failure, n = (%)	-	-	-	-	-	-
	Hypertension, n = (%)	2,911 (74)	2,930 (51)	0.492	1,931 (67)	1,869 (65)	0.046
	Stroke, n = (%)	160 (4)	106 (2)	0.132	94 (3)	75 (3)	0.039
Lipid levels	LDL-C mg/dl	92.8 ± 39.9	75.5 ± 28.5	-	98.5 ± 41.0	74.0 ± 28.5	-
	LDL-C, missing n = (%)	517 (13)	2,130 (37)	-	268 (13)	928 (32)	-
Drug treatment	Statin	1731 (44)	963 (17)	0.621	906 (32)	800 (28)	0.084

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; LOS, length of stay;

Table 2. Results of 4 sensitivity analysis by separate Cox proportional regression models among patients with acute myocardial infarction or heart failure in whom the relevant data point were available. Model 1, propensity-score matched patients with available data on BMI; Model 2, propensity-score matched patients with available data on LVEF; Model 3, propensity-score matched patients with available data on LDL-C measured on admission or within the preceding 6 –months; Model 4, propensity-score matched patients with available data on sodium, BUN, and creatinine levels measured on admission.

Acute myocardial infarction

Variables	Model 1 HR (95% CI) P value	Model 2 HR (95% CI) P value	Model 3 HR (95% CI) P value	Model 4 HR (95% CI) P value
Age	1.06 (1.05 – 1.06) <0.0001	1.07 (1.06 – 1.07) <0.0001	1.06 (1.05 – 1.06) <0.0001	1.06 (1.05 – 1.06) <0.0001
Gender	1.06 (0.99 – 1.14) 0.1123	1.04 (0.96 – 1.13) 0.3128	1.07 (0.99 – 1.14) 0.0650	1.07 (0.96 – 1.11) 0.3931
Ethnicity	0.79 (0.71 – 0.89) 0.0001	0.76 (0.65 – 0.89) 0.0006	0.735 (0.67 – 0.87) 0.9286	0.83 (0.75 – 0.92) 0.0003
Length of stay	1.01 (1.01 – 1.02) <0.0001	1.01 (1.01 – 1.02) <0.0001	1.02 (1.01 – 1.02) <0.0001	1.00 (0.99 – 1.01) 0.1374
Cancer vs no cancer	1.82 (1.62 – 2.05) <0.0001	2.08 (1.82 – 2.39) <0.0001	1.77 (1.57 – 1.99) <0.0001	1.76 (1.56 – 1.99) <0.0001
CKD vs no CKD	1.67 (1.49 – 1.86) <0.0001	1.88 (1.66 – 2.13) <0.0001	1.47 (1.31 – 1.64) <0.0001	
COPD vs no COPD	1.64 (1.50 – 1.81) <0.0001	1.78 (1.60 – 1.98) <0.0001	1.75 (1.60 – 1.91) <0.0001	1.58 (1.44 – 1.74) <0.0001
DM vs no DM	1.48 (1.37 – 1.60) <0.0001	1.51 (1.51 – 1.39) <0.0001	1.45 (1.35 – 1.56) <0.0001	1.38 (1.28 – 1.49) <0.0001
HLP vs no HLP	0.74 (0.70 – 0.80) <0.0001	0.77 (0.72 – 0.83) <0.0001		0.76 (0.71 – 0.82) <0.0001
HF vs no HF	1.65 (1.52 – 1.78) <0.0001	1.54 (1.40 – 1.69) <0.0001	1.65 (1.54 – 1.78) <0.0001	1.55 (1.43 – 1.68) <0.0001
HTN vs no HTN	0.96 (0.89 – 1.03) 0.3022	1.01 (0.93 – 1.09) 0.8735	0.95 (0.89 – 1.02) 0.0.1532	0.85 (0.79 – 0.91) <0.0001
Stroke vs no stroke	1.32 (1.12 – 1.57) 0.0004	1.20 (0.98 – 1.46) 0.0735	1.28 (1.09 – 1.51) 0.0060	1.45 (1.23 – 1.71) <0.0001
BMI	0.99 (0.98 – 0.99) 0.0130			
LVEF < 50% vs ≥ 50%		1.36 (1.26 – 1.48) <0.0001		
Sodium, ≤135 vs > 135 mmol/l				1.12 (1.03 – 1.22) 0.0055
BUN ≤ 19 vs ≥20 mg/dl				0.79 (0.73 – 0.85) <0.0001
Creatinine ≤1.5 vs >1.5 mg/dl				0.66 (0.55 – 0.66) <0.0001
LDL-C, Q2 vs Q1			0.90 (0.83 – 0.99) 0.0240	
LDL-C, Q3 vs Q1			0.87 (0.79 – 0.95) <0.0033	
LDL-C, Q4 vs Q1			0.83 (0.75 – 0.92) <0.0003	

Heart Failure

Variables	Model 1 HR (95% CI) P value	Model 2 HR (95% CI) P value	Model 3 HR (95% CI) P value	Model 4 HR (95% CI) P value
Age	1.03 (1.03 – 1.04) <0.0001	1.04 (1.04 – 1.05) <0.0001	1.03 (1.03 – 1.04) <0.0001	1.04 (1.03 – 1.04) <0.0001
Gender	1.10 (1.03 – 1.19) 0.0010	1.11 (1.01 – 1.21) 0.0264	1.07 (0.98 – 1.15) 0.1144	1.02 (0.93 – 1.11) <0.0001
Ethnicity	1.18 (1.04 – 1.35) 0.0119	1.05 (0.87 – 1.25) 0.6243	1.14 (1.00 – 1.31) <0.0462	1.13 (0.97 – 1.32) 0.1155
Length of stay	1.02 (1.01 – 1.02) <0.0001	1.02 (1.01 – 1.02) <0.0001	1.02 (1.01 – 1.02) <0.0001	1.04 (1.01 – 1.02) 0.0005
Cancer vs no cancer	1.43 (1.30 – 1.57) <0.0001	1.44 (1.28 – 1.62) <0.0001	1.34 (1.19 – 1.49) <0.0001	1.41 (1.25(1.59) <0.0001
CKD vs no CKD	1.50 (1.39 – 1.62) <0.0001	1.72 (1.56 – 1.89) <0.0001	1.48 (1.36 – 1.62) <0.0001	
COPD vs no COPD	1.16 (1.07 – 1.26) 0.0004	1.25 (1.13 – 1.39) <0.0001	1.19 (1.08 – 1.30) 0.0002	1.23 (1.11 – 1.36) <0.0001
DM vs no DM	1.14 (1.06 – 1.23) 0.0005	1.13 (1.03 – 1.23) 0.0068	1.08 (1.00 – 1.17) 0.0450	1.08 (0.99 – 1.18) 0.0769
HLP vs no HLP	0.81 (0.76 – 0.87) <0.0001	0.83 (0.76 – 0.90) <0.0001		0.78 (0.72 – 0.85) <0.0001
CAD vs no CAD	1.03 (0.96 – 1.10) 0.4144	1.04 (0.96 – 1.14) 0.3457	1.02 (0.94 – 1.11) 0.5854	1.05 (0.96 – 1.14) 0.2684
HTN vs no HTN	0.97 (0.90 – 1.05) 0.4229	0.99 (0.90 – 1.08) 0.8029	0.95 (0.87 – 1.03) 0.2073	0.83 (0.85 – 1.02) 0.1386

Stroke vs no stroke	1.05 (0.86 – 1.28) 0.6273	1.17 (0.94 – 1.46) 0.1605	1.06 (0.86 – 1.30) 0.5812	1.01 (0.80 – 1.28) 0.9253
BMI	0.99 (0.98 – 0.99) <0.0001			
LVEF < 50% vs ≥ 50%		1.07 (0.98 – 1.17) 0.1328		
Sodium, ≤135 vs > 135 mmol/l				1.35 (1.23 – 1.48) <0.0001
BUN ≤ 19 vs ≥20 mg/dl				0.83 (0.74 – 0.92) 0.0007
Creatinine <1.5 vs ≥1.5 mg/dl				0.76 (0.70 – 0.84) <0.0001
LDL-C, Q2 vs Q1			0.89 (0.81 – 0.98) 0.0197	
LDL-C, Q3 vs Q1			0.82 (0.74 – 0.92) <0.0003	
LDL-C, Q4 vs Q1			0.77 (0.68 – 0.87) <0.0001	

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HLP, hyperlipidemia; HR, hazard ratio; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; Q, quartile.

Figures legends

Figure 1. Kaplan-Meier estimates, cumulative incidence of death in propensity-score matched patients

Figure 2. Cox proportional hazard regression models and Forest plot. Hazard ratio (HR) and 95% Confidence Intervals (CI) for all-cause mortality

Figure 3. Results of meta-analysis for all-cause mortality

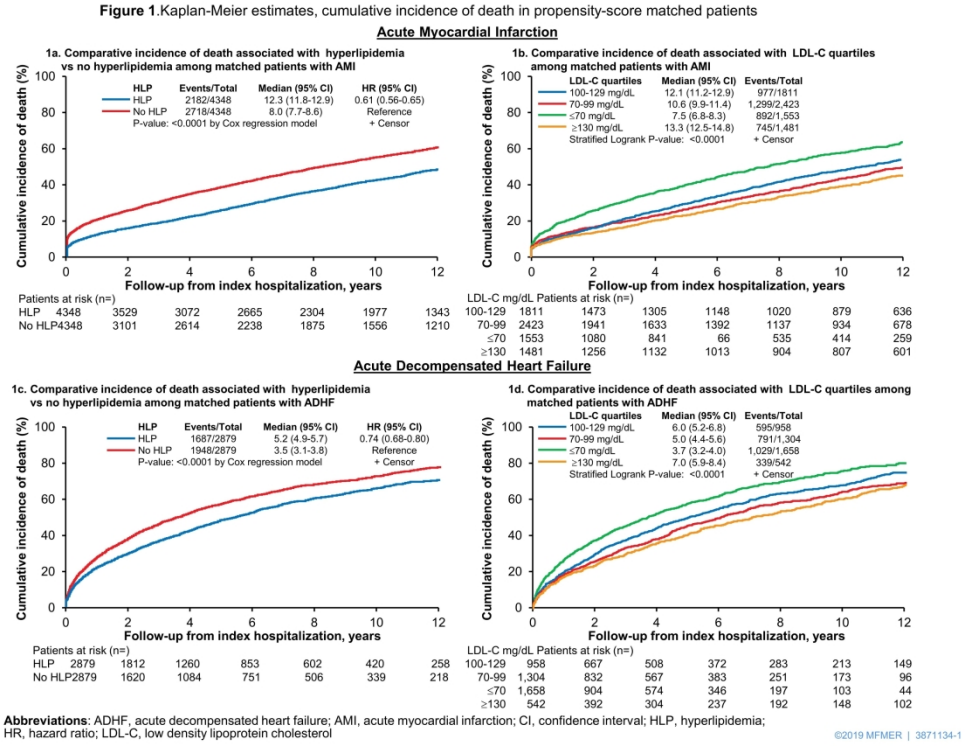

Figure 1

254x190mm (300 x 300 DPI)

Figure 2: Cox proportional hazard regression models and Forest plot. Hazard ratio (HR) and 95% Confidence Intervals (CI) for all-cause mortality.
Figure 2A: Propensity score-matched acute myocardial infarction cohort

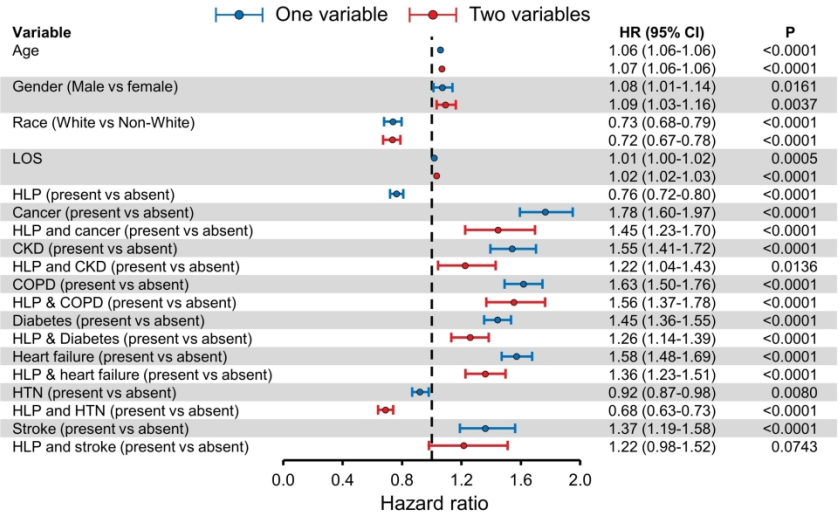

Figure 2B: Propensity score-matched heart failure cohort

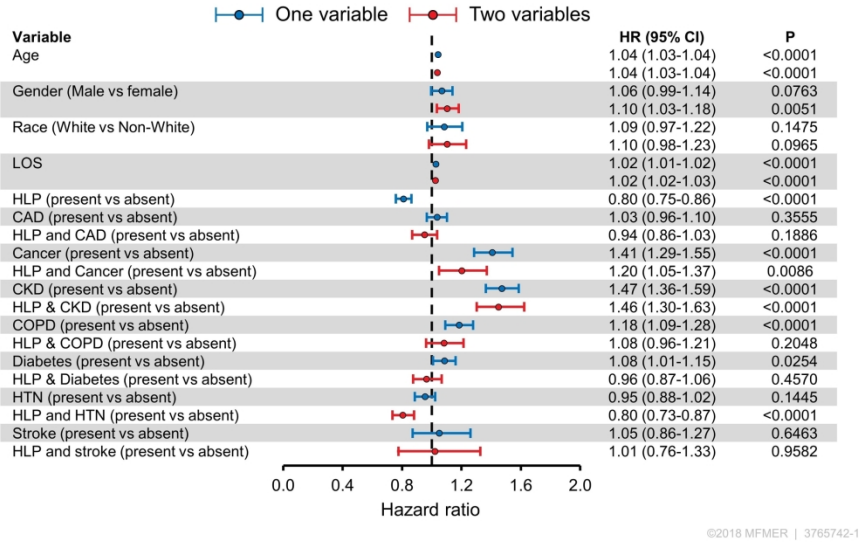

Figure 2

190x254mm (300 x 300 DPI)

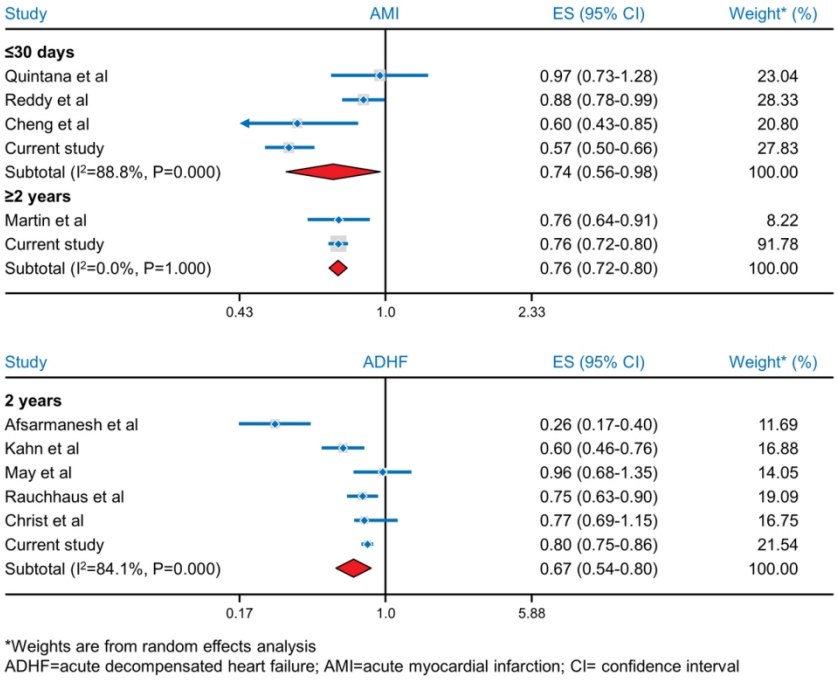

Figure 3

127x95mm (300 x 300 DPI)

Supplementary Material

Title:

Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

Study coauthors:

Mohammed Yousufuddin, Paul Y. Takahashi, Brittny Major, Eimad Ahmmad, Hossam Al-Zu'bi, Jessica L. Peters, Taylor Doyle, Kelsey Jensen, Ruaa Y. Al Ward, Umesh Sharma, Ashok Seshadri, Zhen Wang, Vinaya Simha, M Hassan. Murad.

SEARCH STRATGY

Ovid search strategy

Database(s): Embase 1988 to 2018 Week 08, EBM Reviews - Cochrane Central Register of Controlled Trials January 2018, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

#	Searches	Results
1	exp Myocardial Infarction/	464828
2	exp heart infarction/	293249
3	(("coronary arter*" adj3 occlusion) or (heart adj2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*").ti,ab,hw,kw.	606258
4	1 or 2 or 3	608529
5	acute.ti,ab,hw,kw. and 4	239685
6	exp Heart Failure/	498877
7	(((heart or cardiac or myocardial) adj2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis").ti,ab,hw,kw.	519250
8	6 or 7	633042
9	exp Pneumonia/	313860
10	("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*").ti,ab,hw,kw.	533949
11	9 or 10	549542
12	5 or 8 or 11	1350218
13	exp Hyperlipidemias/	192450
14	("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or	252850

	"xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex").ti,ab,hw,kw.	
15	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu, dt	80348
16	(Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*).ti,ab,hw,kw.	208226
17	Dyslipidemias/	20270
18	(dyslipidemia or dyslipoproteinemia).ti,ab,hw,kw.	92147
19	or/13-18	481133
20	12 and 19	47704
21	exp survival/	902536
22	exp death/	717663
23	exp mortality/	1191292
24	mortality.fs.	506650
25	exp survival analysis/	274790
26	(surviv* or death* or mortalit* or fatalit*).ti,ab,hw,kw.	5314876
27	or/21-26	5623459
28	20 and 27	24286
29	(exp animals/ or exp nonhuman/) not exp humans/	8998409
30	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.	7727415
31	28 not (29 or 30)	23991

32	limit 31 to english language	22671
33	limit 32 to (conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,CCTR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	4951
34	32 not 33	17720
35	exp controlled study/	5856381
36	exp Randomized Controlled Trial/	924372
37	exp triple blind procedure/	179
38	exp Double-Blind Method/	405536
39	exp Single-Blind Method/	72408
40	exp latin square design/	348
41	exp Placebos/	330956
42	exp Placebo Effect/	10111
43	exp comparative study/	2771403
44	exp intervention studies/	34956
45	exp Cross-Sectional Studies/	500737
46	exp Cross-Over Studies/	128902
47	exp Cohort Studies/	2186646
48	exp longitudinal study/	344882
49	exp retrospective study/	1277886
50	exp prospective study/	963919
51	exp clinical trial/	2029131
52	clinical study/	106532
53	exp case-control studies/	1046859
54	exp confidence interval/	162834
55	exp multivariate analysis/	475730
56	((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (random* adj1 allocat*) or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or	18012184

	"case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*)).mp,pt.	
57	or/35-56	18453897
58	34 and 57	14467
59	exp *Hyperlipidemias/ or exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/tu, dt or *Dyslipidemias/ or ("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex" or (Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*) or (dyslipidemia or dyslipoproteinemia)).ti.	170773
60	exp *Myocardial Infarction/ or exp *heart infarction/ or exp *Heart Failure/ or exp *Pneumonia/ or (("coronary arter*" adj3 occlusion) or (heart adj2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*" or (((heart or cardiac or myocardial) adj2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis") or ("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*")).ti.	716170
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64	61 not 62	4255
65	remove duplicates from 64	3291

66 63 or 65	5308
67 5 and 66	2924
68 from 67 keep 1-1890	1890
69 from 68 keep 1-1000	1000
70 from 68 keep 1001-1890	890
71 from 67 keep 1950-2924	975
72 from 67 keep 1891-1949	59
73 66 not 67	2384
74 8 and 73	2199
75 from 74 keep 1-1654	1654
76 from 75 keep 1-1000	1000
77 from 75 keep 1001-1654	654
78 from 74 keep 1655-1710	56
79 from 74 keep 1711-2199	489
80 73 not 74	185
81 from 80 keep 1-100	100
82 from 80 keep 111-185	75
83 from 80 keep 101-110	10

Scopus search strategy

1	TITLE(("coronary arter*" W/3 occlusion) or (heart W/2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*") AND TITLE-ABS-KEY(acute)
2	TITLE(((heart or cardiac or myocardial) W/2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis")
3	TITLE("acute chest syndrome" or Bronchopneumonia* or "inflammatory lung disease*" or lobitis or "lung inflammation*" or pleuropneumonia* or pleuropneumonitis or "pneumonia pleuritica" or "pneumonia superficialis" or pneumonia* or "pneumonic lung*" or "pneumonic pleurisy" or "pneumonic pleuritis" or pneumonitides or pneumonitis or "pulmonal inflammation*" or "pulmonary inflammation*" or "pulmonic inflammation*")
4	1 or 2 or 3
5	TITLE("Buerger Gruetz syndrome" or "Burger Grutz syndrome" or cholesteremia* or cholesterinemia* or cholesterolemia* or "familial hyperbetalipoproteinaemia*" or "familial hyperbetalipoproteinemia*" or "familial hypercholesterolemic xanthomatos*" or "familial hyperlipoproteinaemia type ii" or "familial hyperlipoproteinemia type ii" or "harbitz mueller syndrome" or "hyper low density lipoproteinaemia*" or "hyper low density lipoproteinemia*" or hyperbetalipoproteinaemia* or hyperbetalipoproteinemia* or hypercholesteremia* or hypercholesterinaemia* or hypercholesterinemia* or hypercholesterolaemia* or "hypercholesterolaemic xanthomatos*" or hypercholesterolemia* or "hypercholesterolemic xanthomatos*" or hyperlipaemia* or hyperlipemia* or hyperlipidaemia* or hyperlipidemia* or hyperlipidemic or hyperlipoproteinaemia* or hyperlipoproteinemia* or hypertriglyceridaemia* or hypertriglyceridemia* or "hypertriglyceridemic waist" or "ldl receptor disorder" or lipaemia* or lipemia* or lipidaemia* or lipidemia* or "lipoid gout" or "mckusick 14389" or "mckusick 14430" or "mckusick 14440" or "mckusick 14575" or "tendinous xanthogranulomatos*" or "tendinous xanthomatos*" or "tendon xanthogranulomatos*" or "triglyceride storage disease" or triglyceridemia* or "xanthogranulomatosis tendinosum" or "xanthogranulomatosis tendinous" or "xanthoma tendinosum" or "xanthoma tuberosum" or "xanthoma tuberosum multiplex")
6	TITLE(Atorvastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or fluindostatin* or glenvastatin* or "HMG CoA reductase inhibitor" or "hmg coenzyme a reductase inhibitor" or "hmg-coa reductase inhibitor" or "hydroxymethylglutaryl coa reductase inhibitor" or "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-coa inhibitor" or "hydroxymethylglutaryl-coa reductase inhibitor" or "hydroxymethylglutaryl-coenzyme a inhibitor" or Lovastatin* or Meglutol or mevinolin* or "mevinolinic acid" or "monacolin J" or "monacolin L" or pitavastatin* or Pravastatin* or rosuvastatin* or Simvastatin* or statin* or statins or tenivastatin* or vastatin*)
7	TITLE(dyslipidemia or dyslipoproteinemia)
8	5 or 6 or 7
9	TITLE-ABS-KEY(surviv* or death* or mortalit* or fatalit*)
10	LANGUAGE(english)
11	TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (random* W/1 allocat*) or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or

	"concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*))
12	4 and 8 and 9 and 10 and 11
13	TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))
14	12 and not 13
15	DOCTYPE(ab) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
16	14 and not 15
17	PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
18	16 and not 17
19	TITLE(("coronary arter*" W/3 occlusion) or (heart W/2 (infarct* or necrosis)) or "cardiac infarct*" or "cardial infarct*" or "cardiogenic shock" or "dressler syndrome" or "heart attack*" or "myocardial infarct*" or "myocardial stunning" or "myocardium infarct*" or "premonitory infarction sign" or "subendocardial infarct*") AND TITLE-ABS-KEY(acute)
20	18 and 19
21	TITLE(((heart or cardiac or myocardial) W/2 (failure or decompensat* or insufficienc* or incompetence)) or "cardio-renal syndrome*" or "cardiorenal syndrome*" or "paroxysmal dyspnea*" or "decompensatio cordis" or "insufficientia cardis")
22	(18 and not 20) and 21
23	18 and not (20 or 22)

SUPPLEMENT TABLE 1

Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for index conditions used in the study.

Diagnosis	*ICD-9-CM* Codes
Acute myocardial infarction	410.00, 410.01, 410.10, 410.11, 410.20, 410.21, 410.30, 410.31, 410.40, 410.41, 410.50, 410.51, 410.60, 410.61, 410.70, 410.71, 410.80, 410.81, 410.90, 410.91
Heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40,

SUPPLEMENT TABLE 2. Characteristics of studies and participants included in meta-analysis

Condition	F/U	Study	Year	Design	N =	Mean age, year	Lipid type	End point	Covariates
AMI	≤30-day	Quintana et al[1]	2016	Retrospective cohort	1905		Hyperlipidemia	Death	sex, age, current smoking, parental history of premature cardiac death, general comorbidity, educational level, low disposable income, hypertension, hyperlipidemia, diabetes, overweight and obesity
		Cheng et al[2]	2015	observational study	724	68	LDL-C, TG-C	Death	Age, HTN, DM, smoking, family history of CAD, alcohol consumption, ESRD
		Reddy et al[3]	2015	Observational /Registry	115492	67	LDL-C, HDL-C	Death	Age, sex, race, HTN, previous CAD, DM, smoking, blood pressure, heart rate , previous PCI, previous CABG
		Current study	2018	Retrospective cohort	8,696	68	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use
	≥ 2 years	Martin et al[4]	2015	Prospective Substudy	2465	58	RLP-C, IDL-C, VLDL3-C, VLDL-C	Death	Age, sex, race, education, insurance, history of CAD, Dyslipidemia, DM, blood pressure, CKD, HF, CAD, prior PCI, Prior CABG, Smoking, BMI, activity time, alcohol use
		Current study	2018	Retrospective cohort	8,696	68	HLP	Death	Age, sex, race, BMI, length of stay, lipid levels, CAD, cancer, CKD, COPD, DM, HF, HTN, stroke, statin use
Heart Failure	≥ 2 years	Afsarmanesh et al[5]	2006	Observational cohort	614	48	TC, LDL-C, HDL-C, TG-C	Death	Sex, age, HF etiology, NYHA, DM, smoking, HTN, BMI, LVEF
		Christ et al[6]	2005	Prospective cohort	422	50	LDL-C	Death	Age, sex, race, education, insurance, history of CAD, dyslipidemia, DM, blood pressure, CKD, HF, CAD, prior PCI, Prior CABG, Smoking, BMI, activity time, alcohol use
		Kahn et al[7]	2013	Observational study	2428	69.8	TC, LDL-C, HDL-C, TG-C	Death	Age, sex, HTN, DM, dyslipidemia, smoking, CKD, Cirrhosis, Statin use, BB use, ACE use, hydralazine use, nitrates use, Digoxin use, lipid level, sodium, hemoglobin, Creatinine, BUN, ALT, AST, albumin
		May et al[8]	2006	Registry	1641	65.5	TC, LDL-C, HDL-C, TG-C	Death	Age, sex, HTN, DM, family history of CAD, smoker, previous CAD, previous CVA, statin use, renal function ,BMI, ejection fraction
		Rauchhaus et al[9]	2003	Prospective cohort	303	62	TC	Death	Age, BMI, sodium, potassium, ESR, TNF, BUN, LVEF, lipid level, NYHA class, Cachexia, medication use (loop diuretics, ACE inhibitor, calcium channel blocker, digoxin, amiodarone, BB, lipid lowering, aspirin)

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AMI, acute myocardial infarction; AST, aspartate aminotransferase; BB, beta blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CABG, Coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, Chronic Obstructive Pulmonary Disease; CVA, cerebrovascular accident; DM, Diabetes mellitus; ESRD, end stage renal disease; F/U, follow up; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; HLP, hyperlipidemia; HTN, hypertension; IDL-C, Intermediate-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; N=, number of patients; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RLP-C , remnant-like particles-cholesterol; TC, total cholesterol; TG-C, triglyceride-cholesterol; TNF, tumor necrosis factor; VLDL-C, very-low-density lipoprotein-cholesterol.

References

1. Quintana h, janszky,I, Gigante, B, Druid,H, Ahlbom,A, Hallquist,J, de Faire,U, Leander,K. Diabetes, hypertension, overweight and hyperlipidemia and 7-day case-fatality in first myocardial infarction. *IJC Metabolic & Endocrine.* 2016;12:30-35.
2. Cheng KH, Chu CS, Lin TH, Lee KT, Sheu SH, Lai WT. Lipid paradox in acute myocardial infarction-the association with 30-day in-hospital mortality. *Crit Care Med.* 2015;43(6):1255-1264.
3. Reddy VS, Bui QT, Jacobs JR, et al. Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). *Am J Cardiol.* 2015;115(5):557-562.
4. Martin SS, Faridi KF, Joshi PH, et al. Remnant Lipoprotein Cholesterol and Mortality After Acute Myocardial Infarction: Further Evidence for a Hypercholesterolemia Paradox From the TRIUMPH Registry. *Clin Cardiol.* 2015;38(11):660-667.
5. Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J.* 2006;152(6):1077-1083.
6. Christ M, Klima T, Grimm W, Mueller HH, Maisch B. Prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy. *Eur Heart J.* 2006;27(6):691-699.
7. Kahn MR, Kosmas CE, Wagman G, et al. Low-density lipoprotein levels in patients with acute heart failure. *Congest Heart Fail.* 2013;19(2):85-91.
8. May HT, Muhlestein JB, Carlquist JF, et al. Relation of serum total cholesterol, C-reactive protein levels, and statin therapy to survival in heart failure. *Am J Cardiol.* 2006;98(5):653-658.
9. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42(11):1933-1940.

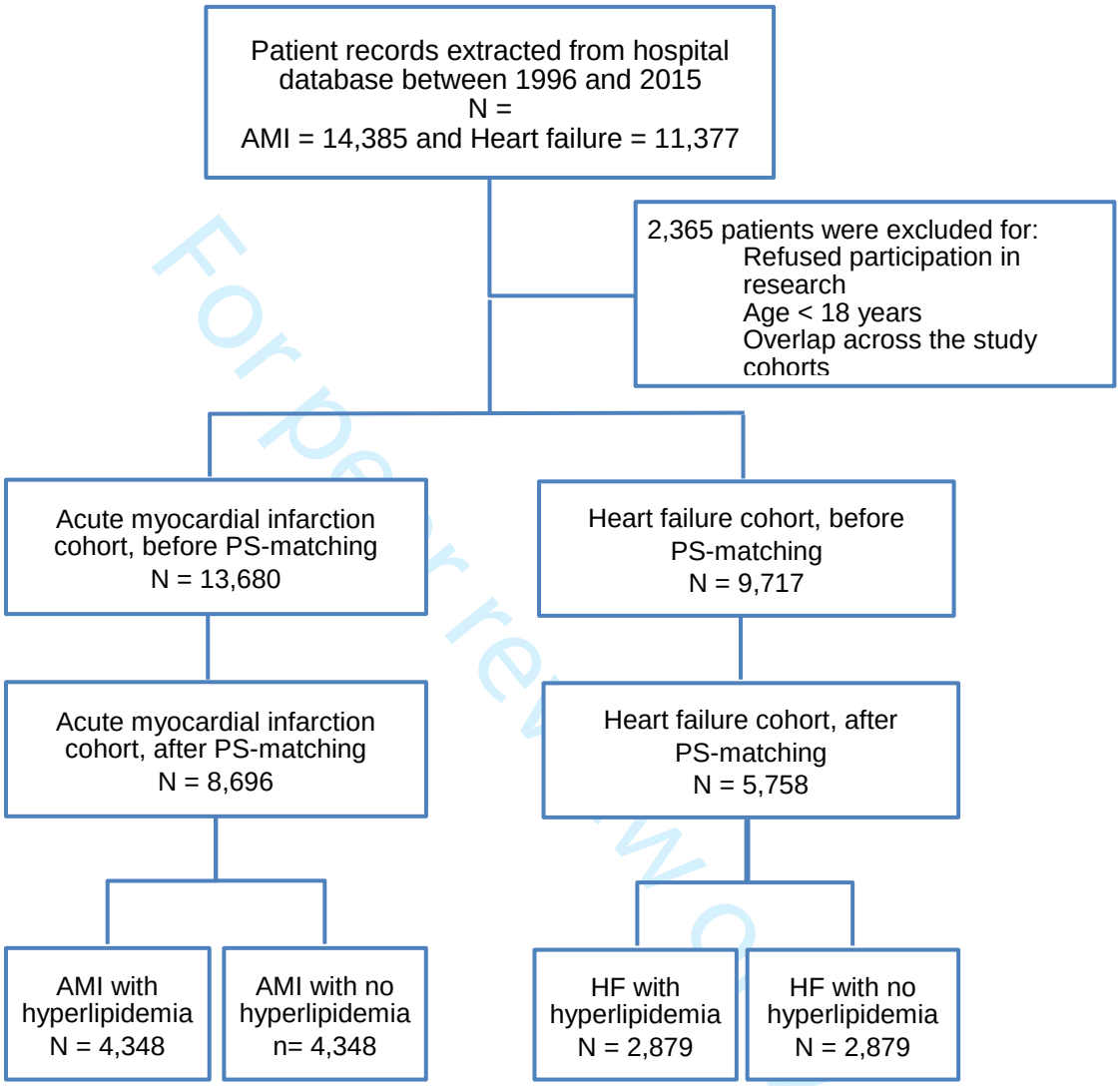
SUPPLEMENT TABLE 3. Risk of Bias Assessment (Newcastle-Ottawa Scale

			Selection				Compatibility		Outcome			
Condition	Study	Year	S1	S2	S3	S4	C1	C2	O1	O2	O3	Quality
Acute Myocardial Infarction	Quintana et al[1]	2016	*	*	*		*	*	*	*	*	8
	Cheng et al[1]	2015	*	*	*		*	*	*			6
	Martin et al[2]	2015	*	*	*		*	*	*	*		7
	Reddy et al[3]	2015	*	*	*		*	*	*	*		7
Heart failure	Afsarmanesh et al[4]	2006	*	*	*		*	*	*	*	*	8
	Christ et al[5]	2005		*	*		*		*	*		5
	Kahn et al[6]	2013	*	*	*		*	*	*	*	*	8
	May et al[7]	2006	*	*	*	*	*	*	*	*	*	9
	Rauchhaus et al[8]	2003	*	*	*		*	*	*	*		7

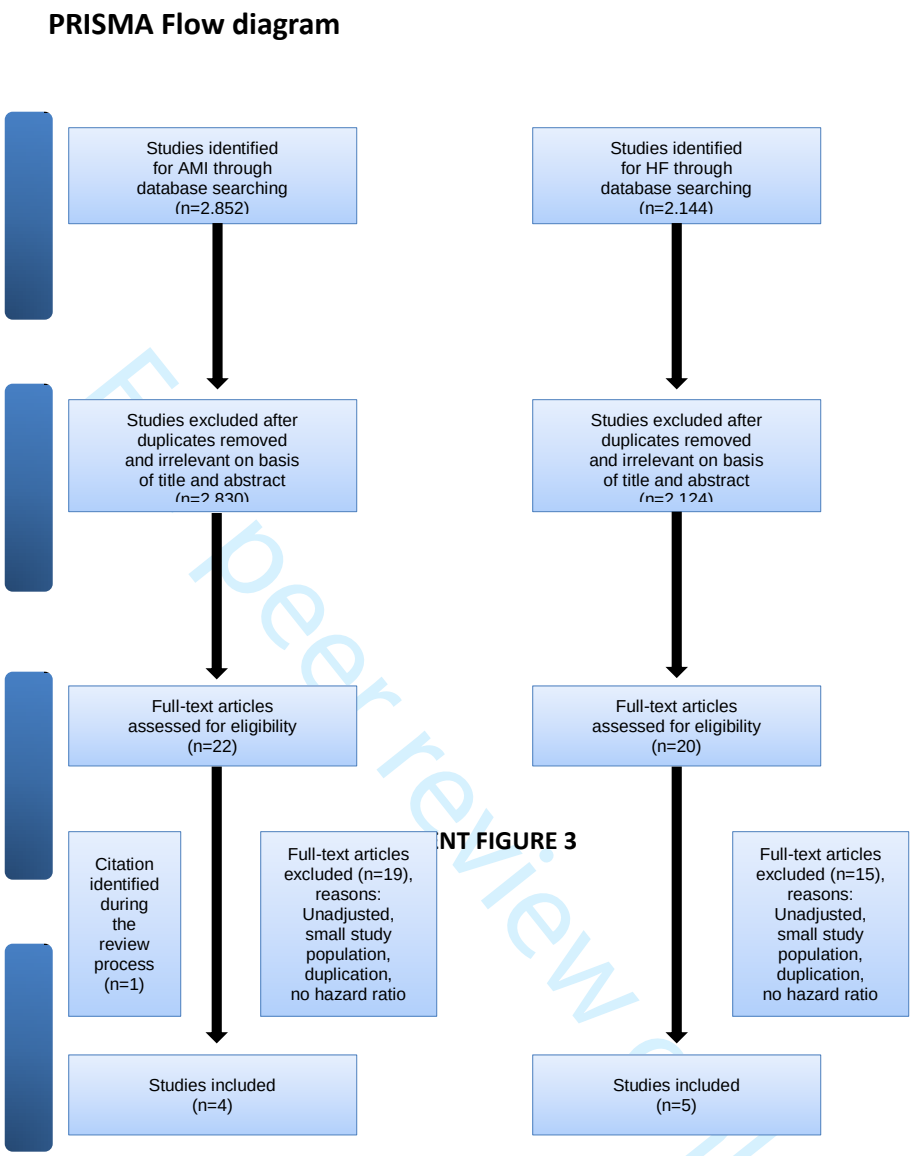
NOTE: S1 = Representativeness of the exposed cohort. S2 = Selection of the non-exposed cohort. S3 = Ascertainment of exposure. S4 = Demonstration that the outcome of interest was not present at the start of the study. C1 = Comparability of the cohort on the basis of design. C2 = Comparability of the cohort on the basis of analysis. O1 = Assessment of outcome. O2 = was the follow-up long enough for outcomes to occur? O3 = Adequacy of the follow-up of cohorts.

SUPPLEMENT FIGURE 1

Flow diagram. **STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram of the process of selection of study cohorts from Mayo Clinic Hospital Data Base**

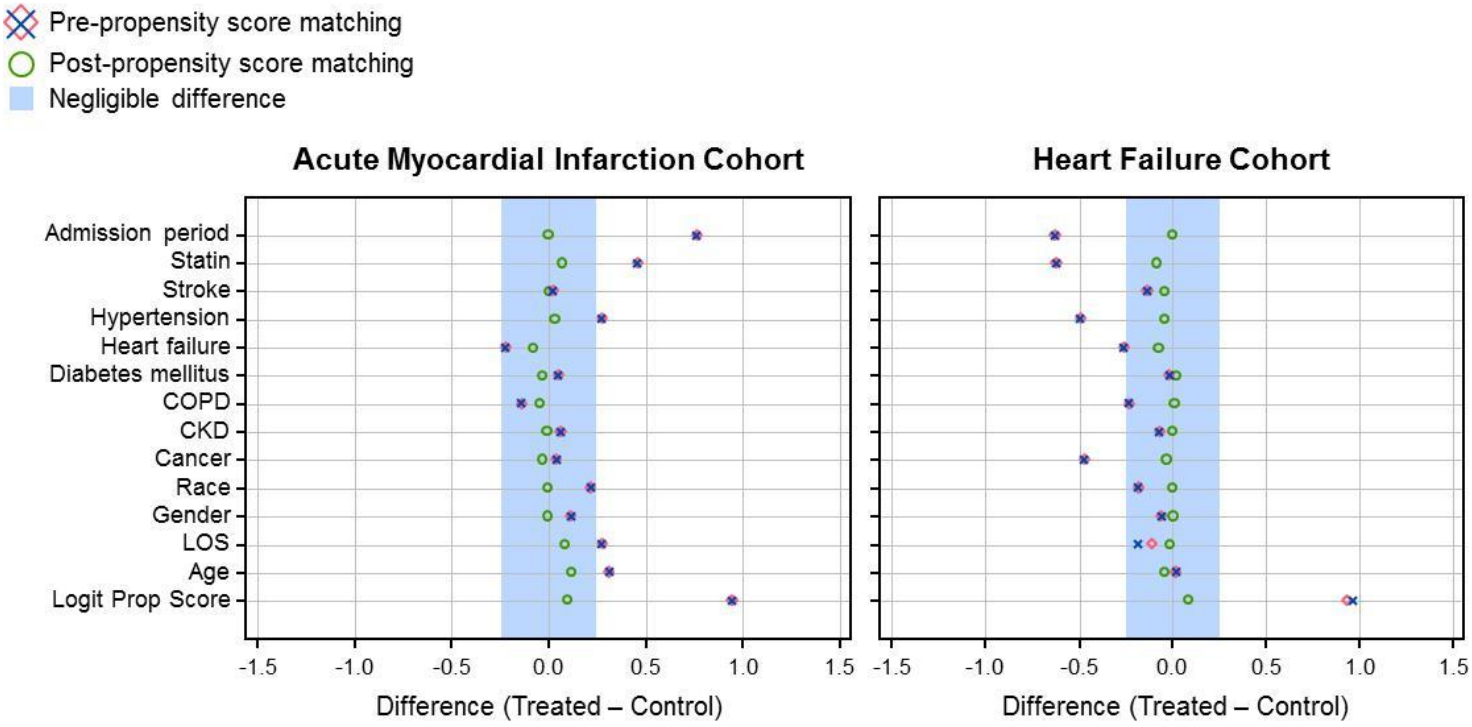


SUPPLEMENT FIGURE 2



NT FIGURE 3

Love plot showing standardized differences for baseline covariates comparing original propensity-score unmatched to propensity-score matched samples, acute myocardial infarction cohort (left panel) and heart failure cohort (right panel)



Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LOS, length of hospital stay

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Title:

Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

Journal: *BMJ Open*

Original title of the manuscript: Hyperlipidemia is associated with lower mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity matched cohort study and a meta-analysis

Manuscript ID #: bmjopen-2018-028638

Authors: Mohammed Yousufuddin, Paul Takahashi, Brittny Major, Eimad M. Ahmmad, Hossam M. Al-Zu'bi, Jessica Shultz,Taylor Doyle, Kelsey Jensen, Umesh Sharma, Zhen Wang, Vinaya Simha, Mohammad H. Murad

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such n/a	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number n/a	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor n/a	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18
INTRODUCTION			

Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6, 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6, 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6, 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6, 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, 6,7 methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup a nalyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6, 7
Confidence in cumulative	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

evidence

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

STROBE Statement

Checklist of items that is included

Title:

Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis

Journal: *BMJ Open*

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Authors: Mohammed Yousufuddin, Paul Takahashi, Brittny Major, Eimad M. Ahmmad, Hossam M. Al-Zu'bi, Jessica Shultz,Taylor Doyle, Kelsey Jensen, Umesh Sharma, Zhen Wang, Vinaya Simha, Mohammad H. Murad

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3, 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7,8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,8
Bias	9	Describe any efforts to address potential sources of bias	8

Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8,9
		(*e*) Describe any sensitivity analyses	8,9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9,10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	10
		Cross-sectional study—Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11,12
		(*b*) Report category boundaries when continuous variables were categorized	9, 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, 12
Discussion			
Key results	18	Summarize key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalizability	21	Discuss the generalizability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.